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Health and Environmental Effects Profile for Carbon Disulfide

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16. ABSTRACT

The Health and Environmental Effects Profile for Carbon Disulfide was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Carbon disulfide has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for carbon disulfide is 0.1 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for carbon disulfide is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CARBON DISULFIDE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constit- uents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Carbon disulfide (CAS Registry number 75-15-0) is a colorless, very flammable and highly volatile liquid, which is produced by high temperature reaction of methane and sulfur gas in the presence of a catalyst (Timmerman, 1978). It is manufactured by Penwalt Corp., PPG, Inc. and Stauffer Chemical Co. (SRI, 1985). USITC (1983) reported that 261.4 million pounds of carbon disulfide was produced in 1982 and that 266.9 million pounds were sold in the United States during 1984 (USITC, 1985). Carbon disulfide is used to manufacture rayon (40%), cellophane (18%) and carbon tetrachloride (15%); miscellaneous other uses (27%) include the manufacture of rubber chemicals and flotation agents, ammonium thiocyanate, sodium thiocyanate, xanthogenates, electronic vacuum tubes, use as an insecticide (fumigant) and as a solvent for phosphorus, sulfur, selenium, bromine, iodine, fats, resins and rubber (CMR, 1983; Berg, 1981; Windholz, 1983). Carbon disulfide has applications as a direct reactant, chemical intermediate and solvent (Timmerman, 1978).

Hydrolysis is not an environmentally significant reaction (Peyton et al., 1978). Peyton et al. (1978) estimated the evaporation $t_{1/2}$ of carbon disulfide from saturated water to be 11 minutes. Henry's law constant indicates volatilization should be a rapid and important removal process. From BCF estimations, it can be predicted that carbon disulfide will not bioaccumulate.

Carbon disulfide does not photolyze under atmospheric conditions (Atkinson et al., 1978; Wood and Heicklen, 1971). Experimental data indicate that carbon disulfide is removed from the troposphere before it can enter

the stratosphere. A range of reaction $t_{1/2}$s was noted for O(^{3}P) oxidation, photooxidation and photohydroxylation of carbon disulfide, but a dominant reaction was not evident because of the variation in available data.

Since carbon disulfide is a soil disinfectant, biodegradation may not be possible. Hydrolysis on wet soil surfaces is also unlikely.

Farwell et al. (1979) monitored the volatilization of carbon disulfide from soils, but the extent of removal by this mechanism was not determined. The predicted behavior of carbon disulfide in water suggests that volatilization from soils could also be potentially significant. Bremner and Banwart (1976) studied the adsorption of gaseous carbon disulfide to soil and suggested that soils are an important natural sink for gaseous atmospheric pollutants, but have little if any potential for removing carbon disulfide from industrial emissions. Based on an estimated K_{oc} value, liquid phase carbon disulfide is expected to be highly mobile in soil (Swann et al., 1983).

The U.S. EPA (1985a) monitored carbon disulfide in whole water, water and sediment samples. Carbon disulfide has been detected in lake, river, ocean and stagnant bay waters, and sea sediments (Kaiser et al., 1983; Lovelock, 1974). Carbon disulfide was also qualitatively identified in drinking waters of three cities and in sewage treatment plant effluents (U.S. EPA, 1974, 1975, 1980).

Carbon disulfide has been found in mother's milk (Pellizzari et al., 1982; Cai and Bao, 1981). Cai and Bao (1981) quantified the amount of carbon disulfide in the mother's milk of employees in rayon factories. Carbon disulfide has also been detected in grains fumigated with carbon disulfide (McMahon, 1971; Alumot and Bielorai, 1969).

The major anthropogenic source of carbon disulfide emission is from viscose rayon manufacturing sites (U.S. EPA, 1980), but the largest global source of atmospheric emissions is from natural sources (Khalil and Rasmussen, 1984). Carbon disulfide is emitted from a wide variety of manmade and natural sources (Hoshika et al., 1975; Graedel, 1978; Beard and Guenzi, 1983; Aneja et al., 1982; Steudler and Peterson, 1984; Farwell et al., 1979; Adams et al., 1979; Lovelock, 1974).

This compound has been identified in the ambient air of rural and urban sites in the United States, in Chicago, IL, Harwell, England and Leningrad, Russia (Brodzinsky and Singh, 1982; Jarke et al., 1981; Sandalls and Penkett, 1977; Ioffe et al., 1977). Based on average atmospheric concentrations in rural and urban areas (Brodzinsky and Singh, 1982), the average daily intakes of carbon disulfide by inhalation are 2.6×10^{-3} and 4.1×10^{-3} mg, respectively. Concentration of carbon disulfide evolving from a cellophane manufacturing plant, shale-retort processes, power plant sludge ponds, oceans, soils and salt marshes have been measured (Umemura et al., 1979; Sklarew et al., 1984; Adams, 1979; Steudler and Peterson, 1984).

Monitoring data regarding dermal exposure could not be located in the available literature as cited in the Appendix.

Limited data regarding the aquatic toxicity of carbon disulfide indicate that concentrations of 30-250 mg/ℓ are toxic to most fish species.

Pertinent data regarding the pharmacokinetics of ingested carbon disulfide could not be located in the available literature as cited in the Appendix.

In humans and animals, carbon disulfide is absorbed rapidly from the lungs; steady-state between inhaled and exhaled carbon disulfide is achieved within 1-2 hours of exposure (Beauchamp et al., 1983; WHO, 1981; McKenna and

DiStefano, 1977; Freundt and Schnapp, 1970; Toyama and Kusano, 1953; McKee et al., 1943). Studies using rats and mice (McKenna and DiStefano, 1977; Bergman et al., 1984) indicate that both unchanged carbon disulfide and its metabolites are rapidly distributed to body fat and highly perfused tissues. Free carbon disulfide is eliminated more rapidly from the tissues than are its metabolites (McKenna and DiStefano, 1977), and neither free carbon disulfide nor its metabolites appear to bioaccumulate in any tissue. Danielsson et al. (1984) also showed that carbon disulfide and its metabolites can cross the placenta throughout gestation, with metabolites accumulating in the bone, liver and neuroepithelium of the fetus.

Numerous in vitro and in vivo studies on animals and humans have suggested that carbon disulfide is metabolized by two major routes: by reaction with amino acids or reduced glutathione to form thiocarbamates or conjugated glutathione, and by reaction with cytochrome P450 to form reactive sulfur (McKenna and DiStefano, 1977; Van Doorn et al., 1981; Soucek and Madlo, 1953; Chengelis and Neal, 1980, 1981; Bond and DeMatteis, 1969; Freundt and Dreher, 1969; Hunter and Neal, 1975; Freundt and Kuttner, 1969; Freundt et al., 1976; Mack et al., 1974; DeMatteis and Seawright, 1973; Dalvi et al., 1974, 1975; Dalvi and Neal, 1978; DeMatteis, 1974; Catignani and Neal, 1975), which may further react to form thiourea, carbonyl sulfide or monothiocarbonate (Beauchamp et al., 1983).

Inhaled carbon disulfide is rapidly excreted in expired air, urine and milk. Unchanged carbon disulfide is eliminated primarily through the lungs (10-30% of absorbed carbon disulfide) and secondarily through urine (<1%), while metabolites of carbon disulfide (70-90% of absorbed carbon disulfide) are eliminated more slowly and principally through urine (McKenna and DiStefano, 1977; Soucek, 1957; McKee et al., 1943; Demus, 1964; Soucek and

Pavelkova, 1953; Cai and Bao, 1981; Toyama and Kusano, 1953; Bergman et al., 1984). In humans, pulmonary excretion of carbon disulfide is reported to be a triphasic process that requires up to 97 hours for completion (Soucek and Pavelkova, 1953). In anesthetized rats, pulmonary excretion was a single first-order process with a $t_{1/2}$ of 85 minutes, while Magos et al. (1974) reported a $t_{1/2}$ of 35 minutes for pulmonary excretion of carbon disulfide in unanesthetized rats. In unanesthetized rats, excretion of bivalent sulfur metabolites in the urine was reduced to control levels within 12-14 hours of exposure (McKenna and DiStefano, 1977).

Animal bioassays designed to test the carcinogenicity of carbon disulfide were not located in the available literature cited in the Appendix. An occupational exposure study on mixed-solvent exposure (Checkoway et al., 1984; Wilcosky et al., 1984) suggested an association between carbon disulfide exposure and leukemia. Wilcosky et al. (1984) suggested that the association may be a statistical artifact of the large number of variables examined. In another study, Nurminen and Hernberg (1984) reported that there was no association between exposure to carbon disulfide and the development of any type of cancer. Mutagenicity studies on carbon disulfide have been largely negative (Hedenstedt et al., 1979; Donner et al., 1981; NTP, 1985; Belliles et al., 1980). However, the possibility of weak mutagenicity cannot be ruled out.

Oral teratology studies conducted in CD rats and New Zealand White rabbits (Jones-Price et al., 1984a,b) showed abnormal terata without maternal toxicity (rabbits; 25 mg/kg/day on days 6-19 gestation), which suggests that carbon disulfide does affect the developing fetus. Furthermore, a repeat generation (F_0-F_2) inhalation teratology study in albino rats demonstrated that terata (club foot, hydrocephalus, edema, tail deformation) are observed at lower doses (0.03 or 10 mg/m^3, 8 hours/day

throughout gestation) in successive generations of animals exposed to carbon disulfide (Tabacova et al., 1983). However, because of lack of support from other rodent inhalation teratological studies in the United States and some deficiencies in scientific interpretations of the Tabacova et al. (1983) study, it is suggested that additional multigeneration studies be conducted to better characterize the adverse effects reported above.

Oral reproductive studies of carbon disulfide could not be located in the available literature as cited in the Appendix. Human occupational exposure studies suggest that carbon disulfide may cause disturbances in male sexual dynamics (Cirla et al., 1978; Lancrajan et al., 1969; Lancrajan, 1972), decreases in sperm count (Lancrajan et al., 1969; Lancrajan, 1972), alterations in the menstrual cycle and increases in spontaneous abortion (Petrov, 1969; Vasileva, 1973; Cai and Bao, 1981; Bezvershenko, 1965). Inhalation studies in rats have suggested that carbon disulfide decreases ejaculated sperm count and elicits changes in male copulatory behavior (Zenick et al., 1984a,b; Tepe and Zenick, 1984). The evidence in support of carbon disulfide-induced endocrinological changes is equivocal (Lancrajan et al., 1969; Cirla et al., 1978; Maugeri et al., 1966; Wägar et al., 1983; Cirla and Graziano, 1981; Zenick et al., 1984a; Tepe and Zenick, 1984).

Only two subchronic oral studies were located in the available literature. In the first study, Wistar rats treated by gavage with 25 mg carbon disulfide/kg bw for 60 days developed normochromic, monocytic anemia, eosinopenia and reticulocytosis (Pilarska et al., 1973). In the second study, Wistar rats treated by gavage with either 0.3 mg carbon disulfide/kg bw, 2 times/week for 8 weeks or 0.6 mg carbon disulfide/kg bw for 4, 8, 12 or 20 weeks had histologically-defined damage to nerve fibers in the brain (Dietzmann and Laas, 1977). Since lower doses were not used in either study, a NOEL was not defined.

Subchronic animal inhalation studies demonstrated that carbon disulfide causes neurological effects (Haltia and Linnoila, 1978a,b; Formanek et al., 1976; Maroni et al., 1981; Szendzikowski et al., 1973a,b, 1974; Ferraro et al., 1941; Wood, 1981; Knobloch et al., 1979; Linnoila et al., 1974; Seppalainen and Linnoila, 1975, 1976; Jirmanova and Lukas, 1984; Juntunen et al., 1974, 1977; Lukas, 1979; Lukas et al., 1980; Kulinskaya, 1967; Lewey et al., 1941; Colombi et al., 1981; Richter, 1945); cardiovascular effects (Grodetskaya et al., 1979; Laurman and Wronska-Nofer, 1977; Saitanov et al., 1977; Wronska-Nofer, 1972; Wronska-Nofer and Knobloch, 1972; Wronska-Nofer et al., 1980; Wesolowska, 1979); hepatic effects (Gregorczyk et al., 1975; Cuccurullo et al., 1978); gastrointestinal effects (Murashko and Tantsyura, 1977); renal effects (Cohen et al., 1959; Cuccurullo et al., 1978; Isler, 1957; Salnikova and Chirkova, 1974; Wronska-Nofer and Knobloch, 1972); and hematological effects (Kiczak et al., 1972; Wojewski et al., 1972; Wakatsuki, 1959). Occupational exposure studies and case reports suggested that carbon disulfide may cause neurological effects (Vigliani, 1954; Delpech, 1856; Viscose Rayon Survey, 1938; Peterson, 1892; Hamilton, 1915; Jump and Cruice, 1904; Francine, 1904; Hanninen, 1971; Tuttle et al., 1976; Seppalainen et al., 1972; Seppalainen and Tolonen, 1974; Vasilescu, 1972; Corsi et al., 1983; Johnson et al., 1983; Hirata et al., 1984); cardiovascular effects (Tiller et al., 1968; Hernberg et al., 1970, 1973, 1976; Nurminen, 1976; Tolonen et al., 1975; Nurminen and Hernberg, 1985; Vigliani, 1954; Lieben et al., 1974; Sakurai and Seki, 1977; Cirla et al., 1978; Kramarenko et al., 1971; Franco et al., 1982); ophthalmological effects (Sugimoto et al., 1976a,b, 1978; Goto et al., 1971, 1972; Goto and Hotta, 1967; Hotta et al., 1972; Raitta and Tolonen, 1975; Raitta et al., 1974; Tolonen et al., 1977; Sugimoto et al., 1977; De Laey et al., 1980; De Laey,

1978; Evans et al., 1973; Gilioli et al., 1978; Maugeri et al., 1966); immunological effects (Kashin, 1965); gastrointestinal effects (Vigliani, 1954); and metabolic effects (Kujalova et al., 1979).

In humans as well as in animals, neurological effects occur at the lowest levels of exposure (<2 ppm in humans). A "no-effect level" for chronic toxicity has not been defined in either inhalation studies on animals or in occupational exposure studies.

An RQ of 1000 is recommended based on a CS of 15 derived from the oral teratology study by Jones-Price et al. (1984b). The ADI of 0.1 mg/kg/day, derived on the basis of teratogenic effects (Hardin et al., 1981), is recommended as protective until appropriate oral studies are conducted. The rationale for selecting an ADI based on a teratology study is discussed in Chapter 8.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AEL	Adverse-effect level
ATP	Adenosine triphosphate
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
EKG	Electrocardiogram
FEL	Frank-effect level
FSH	Follicle-stimulating hormone
K_{oc}	Soil sorption coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LH	Luteinizing hormone
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MCV	Motor conduction velocity
MED	Minimum effective dose
MFO	Mixed function oxidase
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PNS	Peripheral nervous system

ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cell
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Carbon disulfide is also known as carbon bisulfide and dithiocarbonic anhydride (U.S. EPA, 1985b). The structure, CAS Registry number, chemical formula and molecular weight are as follows:

$$S = C = S$$

CAS Registry number: 75-15-0

Chemical formula: CS_2

Molecular weight: 76.13

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Carbon disulfide is a clear, colorless, very flammable and highly volatile liquid that has a mild ethereal odor when pure, but a disagreeable sulfurous odor when impure (Timmerman, 1978). Carbon disulfide is miscible with anhydrous methanol, ethanol, ether, benzene, chloroform, carbon tetrachloride and oils (Windholz, 1983). Selected chemical and physical properties are listed below:

Melting point:	-108.6 to -116.6°C	Verschueren, 1983
Boiling point:	46.3°C	Verschueren, 1983
Vapor pressure (at 20°C):	297 mm Hg	Timmerman, 1978
Water solubility (at 20°C):	2940 mg/ℓ	Windholz, 1983
Log K_{ow} (calculated):	2.16	Leo et al., 1971
Density (at 20/4°C):	1.2632	Windholz, 1983
Vapor density (air=1):	2.64	Verschueren, 1983
TLV (skin):	10 ppm	Popendorf, 1984
Flashpoint (closed cup):	-30°C	Windholz, 1983
Odor detection threshold:	0.07 mg/m³	Verschueren, 1983
Conversion factors:	1 mg/m³=0.315 ppm 1 ppm=3.17 mg/m³	Verschueren, 1983

1.3. PRODUCTION DATA

Carbon disulfide is produced by high temperature reaction of methane and sulfur gas in the presence of a catalyst such as charcoal, Cr, W and Mo compounds, and oxides, sulfides of metals (Timmerman, 1978).

According to SRI (1985), the following companies manufactured carbon disulfide as of January, 1985:

Company	Location	Capacity (million pounds/year)
Penwalt Corp.	Green Bayon, TX	10
PPG, Inc.	Natrium, WV	60
Stauffer Chemical Co.	Delaware City, DE	350
	Lemoyne, AL	250

In 1982, 261.4 million pounds of carbon disulfide were produced in the United States (USITC, 1983). Sales for the U.S. in 1984 were 266.9 million pounds of carbon disulfide, but the 1984 production volume was not available (USITC, 1985).

1.4. USE DATA

The use pattern of carbon disulfide is as follows (CMR, 1983):

rayon	40%
cellophane	18%
carbon tetrachloride	15%
miscellaneous (including rubber chemicals, ammonium thiocyanate and sodium thiocyanate)	27%

The miscellaneous category includes a wide variety of uses, such as agricultural and pharmaceutical applications, either as a direct reactant, chemical intermediate or solvent (Timmerman, 1978). Carbon disulfide is an insecticide used for soil and grain fumigation (Berg, 1981). It is also used in

the manufacture of xanthogenates, flotation agents, electronic vacuum tubes and as a solvent for phosphorus, sulfur, selenium, bromine, iodine, fats, resins and rubber (Windholz, 1983).

1.5. SUMMARY

Carbon disulfide is a colorless, very flammable and highly volatile liquid, which is produced by high temperature reaction of methane and sulfur gas in the presence of a catalyst (Timmerman, 1978). It is manufactured by Penwalt Corp., PPG, Inc. and Stauffer Chemical Co. (SRI, 1985). USITC (1983) reported that 261.4 million pounds of carbon disulfide was produced in 1982 and that 266.9 million pounds were sold in the United States during 1984 (USITC, 1985). Carbon disulfide is used to manufacture rayon (40%), cellophane (18%), carbon tetrachloride (15%) and for miscellaneous purposes (27%) (CMR, 1983). Miscellaneous uses include the manufacture of rubber chemicals and flotation agents, ammonium thiocyanate, sodium thiocyanate, xanthogenates, electronic vacuum tubes; use as an insecticide (fumigant) and as a solvent for phosphorus, sulfur, selenium, bromine, iodine, fats, resins and rubber (CMR, 1983; Berg, 1981; Windholz, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. WATER

2.1.1. Hydrolysis. Peyton et al. (1978) reported that carbon disulfide will not hydrolyze in the pH region of environmental concern (pH 4-10). The hydrolysis $t_{1/2}$ at pH 13 is ~1 year, thus extrapolation of this value to pH 9 gives a $t_{1/2}$ of 1.1 years (Peyton et al., 1978).

2.1.2. Oxidation. In oxygenated seawater, carbon disulfide is stable for $\geq$10 days (Lovelock, 1974). Further information on the oxidation of carbon disulfide was not available.

2.1.3. Photolysis. Since carbon disulfide absorbs light of wavelengths >290 nm (Sadtler, n.d.), photodegradation may be possible. U.S. EPA (1985b) reports that carbon disulfide degrades when exposed to sunlight, darkening to a yellow tint. No quantitative estimate about the half-life of this reaction can be made because of the lack of rate data.

2.1.4. Microbial Degradation. Pertinent data regarding the microbial degradation of carbon disulfide in water could not be located in the available literature as cited in the Appendix.

2.1.5. Volatilization. No experimental data regarding the volatilization of carbon disulfide from water were located in the available literature; however, Peyton et al. (1978) used the rate of evaporation approximation and assigned parameters developed by Mackay and Wolkoff (1973) to estimate an evaporation $t_{1/2}$ of 11 minutes from a saturated water solution.

A Henry's law constant of 1.01×10^{-2} atm·m³/mol, calculated from a vapor pressure of 297 mm Hg (at 20°C) and water solubility of 2.94×10^{3} mg/ℓ (at 20°C), indicates volatilization from all waters should be a rapid (Lyman et al., 1982) and important removal process.

2.1.6. **Adsorption.** Pertinent data regarding the adsorption of carbon disulfide to suspended particulates and sediments in water could not be located in the available literature as cited in the Appendix; however, since the K_{oc} value for carbon disulfide is 54 (Section 2.3.), the compound is not expected to be removed significantly from the aquatic phase through adsorption.

2.1.7. **Bioaccumulation.** No experimental bioaccumulation data were located in the available literature; however, BCFs were estimated from the WS and log K_{ow}. Using the equations, log BCF = 2.791 - 0.564 log WS (Kenaga, 1980) and log BCF = 0.76 log K_{ow} - 0.23 (Veith, 1980), the BCF has been calculated to be $\leq$26. Based on this information, carbon disulfide is predicted not to bioaccumulate in aquatic organisms.

2.2. AIR

2.2.1. **Photolysis.** Although carbon disulfide absorbs light wavelengths between 280 and 350 nm, dissociation does not occur under environmental conditions (Atkinson et al., 1978; Wood and Heicklen, 1971). The direct photolysis in the atmosphere may not be significant for carbon disulfide.

2.2.2. **Oxidation.** Khalil and Rasmussen (1984) estimated the lifetime of carbon disulfide in the atmosphere to be 13 days. Removal was suggested to occur by OH• reaction, O atom reaction and other reactions (excluding photolysis). The reaction between carbon disulfide and oxygen atoms is expected to proceed primarily by the following reaction (Slagle et al., 1974):

$$O + CS_2 \rightarrow CS + SO_2$$

Various rate constants reported for the reaction of carbon disulfide with atomic oxygen are 2.53×10^9 $(M\text{-sec})^{-1}$ at 300°K (Hsu et al., 1979), 2.4×10^9 $(M\text{-sec})^{-1}$ at 302°K (Slagle et al., 1974), and 9.15×10^9

$(M\text{-}sec)^{-1}$ at 273°K (Wei and Timmons, 1975), as well as others (Takahashi, 1971; Sze and Ko, 1980; Hampson, 1980; NASA, 1981). Assuming an average tropospheric $O(^3P)$ concentration of 6.0×10^{-17} M (Cupitt, 1980) and the rate constant of 9.15×10^{9} $(M\text{-}sec)^{-1}$ at 273°K (close to average tropospheric temperature), the $t_{1/2}$ for carbon disulfide has been calculated to be ~150 days.

Olszyna and Heicklen (1970) determined that the reaction of ozone with carbon disulfide was rapid at 303°K. The reaction was studied for carbon disulfide pressures from 0.9-80 Torr, initial ozone pressures of 0.15-4.0 Torr and $[CS_2]/[O_3]_0$ ratios from 1.0-530. Peyton et al. (1978) asserts that the results of this study are not amenable to environmental predictions because of the conditions under which this study was performed.

Heicklen et al. (1971) studied the photooxidation of carbon disulfide in the presence of molecular oxygen at an absorption maximum of 313 nm. Products of this reaction were CO, OCS and SO_2, and quantum yields were small, ranging from 3×10^{-4} to 10^{-1}. Based on the maximum quantum yield, Peyton et al. (1978) calculated a mean photooxidation lifetime of 5 days, assuming 12 hours of sunlight/day, while using the minimum quantum yield, the mean lifetime was calculated to be 10 years under similar conditions (Peyton et al., 1978).

The photohydroxylation of carbon disulfide has been evaluated in several studies. Assuming an ambient OH· concentration of 1×10^{6} molecules/cm^3 (Cupitt, 1980) and rate constants of 1.85×10^{-13} at 23°C (Kurylo, 1978), 4.3×10^{-13} at 24°C (Cox and Sheppard, 1980) and 2.7×10^{-12} cm^3/molecule-sec in synthetic air at 20°C (Barnes et al., 1983), the photohydroxylation $t_{1/2}$s have been calculated to be 43, 19 and 3 days, respectively. Atkinson et al. (1978) determined the average photohydroxylation $t_{1/2}$ in the troposphere to be >73 days.

Since a range of reaction half-lives were noted for the reaction of carbon disulfide with O(^{3}P), photooxidation and photohydroxylation, it is difficult to predict the dominating reaction responsible for the removal of atmospheric carbon disulfide. Assuming that the overall lifetime of atmospheric carbon disulfide is 13 days (Khalil and Rasmussen, 1984), and the tropospheric to stratosphera turnover time is 30 years, very little tropospheric carbon disulfide is expected to be transported to the stratosphere.

2.2.3. **Physical Transport.** Pertinent data regarding the physical transport and removal of carbon disulfide in the atmosphere could not be located in the available literature as cited in the Appendix.

2.3. **SOIL**

2.3.1. **Microbial Degradation.** No data were available regarding the microbial degradation of carbon disulfide in soil; however, since this compound is a soil disinfectant and toxic to bacteria, biodegradation may not be a significant fate process.

2.3.2. **Chemical Degradation.** Information in Section 2.1.1. suggests that hydrolysis on wet soil surfaces is unlikely. Although carbon disulfide absorbs light wavelengths >290 nm (Sadtler, n.d.), the likelihood of carbon disulfide photodegradation on soil surfaces in uncertain.

2.3.3. **Volatilization.** Farwell et al. (1979) indicated that carbon disulfide does volatilize from a variety of soils such as Warden loam, Cispus sandy loam and tidal marsh soil. Volatilization rates for carbon disulfide samples applied to these soil surfaces were not available. Carbon disulfide is predicted to volatilize rapidly from water (see Section 2.1.4.), suggesting that volatilization from wet soil surfaces could also be significant.

2.3.4. **Adsorption.** Bremner and Banwart (1976) studied the adsorption of gaseous carbon disulfide on four soil surfaces with organic content

1.73-9.02% and pH 5.5-7.7. The average extent of adsorption in air-dry and moist soils in 10 minutes (100 ppm gas, 5 g soil) was 46 and 12%, respectively. Complete sorption of 100 ppm gas to moist soil occurred in 4-14 days. An experiment with sterilized (autoclaved) soil indicated that soil microorganisms were partly responsible for the sorption of carbon disulfide by moist soils (Bremner and Banwart, 1976). Results of this experiment suggest that soils have little, if any, potential for removing carbon disulfide from industrial emmissions polluted with the compound (Bremner and Banwart, 1976).

Using the method of Kenaga (1980), log K_{oc} = 3.64 - 0.55 log WS, the K_{oc} was calculated to be 54. Thus, aquatic carbon disulfide is predicted to show weak sorption, and therefore, will be highly mobile in soil (Swann et al., 1983).

2.4. SUMMARY

Hydrolysis of carbon disulfide in aquatic media is not an environmentally significant reaction (Peyton et al., 1978). Peyton et al. (1978) estimated the evaporation $t_{1/2}$ of carbon disulfide from saturated water to be 11 minutes. Henry's law constant also indicates volatilization should be a rapid and important removal process. From BCF estimations, it can be predicted that carbon disulfide will not bioaccumulate.

Carbon disulfide does not directly photolyze under atmospheric conditions (Atkinson et al., 1978; Wood and Heicklen, 1971). Experimental data indicate that carbon disulfide is removed from the troposphere before it can enter the stratosphere. A range of reaction $t_{1/2}$s was noted for $O(^3P)$ oxidation, photooxidation and photohydroxylation of carbon disulfide, but a dominant reaction was not evident because of the variation in available data.

Since carbon disulfide is a soil disinfectant, biodegradation may not be significant in soils. Hydrolysis on wet soil surfaces is also unlikely.

Farwell et al. (1979) monitored the volatilization of carbon disulfide from soils, but the half-life of the removal process cannot be determined from the data presented. The predicted behavior of carbon disulfide in water suggests that volatilization from soils could also be potentially significant. Bremner and Banwart (1976) studied the adsorption of gaseous carbon disulfide onto soils and suggested that soils have little if any potential for removing carbon disulfide from industrial emissions. Based on an estimated K_{oc} value, aquatic carbon disulfide is expected to be highly mobile in soil (Swann et al., 1983).

3. EXPOSURE

3.1. WATER

Monitoring data for carbon disulfide obtained from U.S. EPA's STORET data base is presented in Table 3-1. Carbon disulfide has been found in Lake Ontario waters at levels ranging from trace amounts to 3.9 ppm, as well as in Niagara River water at levels of 0-25 ppb (Kaiser et al., 1983). Lovelock (1974) reported that levels of carbon disulfide in the open Atlantic Ocean, in mud at the sea bottom, in the Atlantic Ocean off Ireland and in stagnant bay waters were 0.52, 29.5, 0.78 and 5.4 ng/ℓ, respectively. Lovelock (1974) speculated that the carbon disulfide originated under anaerobic conditions on the sea floor. Riley et al. (1980) quantitatively identified carbon disulfide in water from the Puget Sound. Carbon disulfide was identified but not quantified in drinking waters of Miami, FL, Cincinnati, OH (U.S. EPA, 1975) and New Orleans, LA (U.S. EPA, 1974), and in sewage treatment plant effluents (U.S. EPA, 1980).

3.2. FOOD

Carbon disulfide has been qualitatively identified in the mother's milk of women from Bayonne, NJ, Jersey City, NJ, Bridgeville, PA, and Baton Rouge, LA (Pellizzari et al., 1982). Cai and Bao (1981) analyzed milk from 17 breast-feeding employees during working hours at rayon factories. Carbon disulfide concentrations of 6.8-12.3 μg/100 mℓ mother's milk were measured. Furthermore, contamination of milk was detected after work, the next morning before work and even 23-57 days away from the job. Levels of 0.8-2.2 ppm carbon disulfide (McMahon, 1971) and 0-500 ppm (Alumot and Bielorai, 1969) have been found in various grains fumigated with carbon disulfide. Alumot and Bielorai (1969) measured decreasing concentrations of carbon disulfide in grain aired for an increasing number of days, after fumigation.

TABLE 3-1

Monitoring Data for Carbon Disulfide*

	Concentration of Carbon Disulfide		
	Whole Water (µg/ℓ)	Water (µg/kg)	Sediment (total µg/ℓ)
Number of Stations	117	8	6
Maximum	348.00	20.00	13.20
Minimum	0.00	5.00	4.00
Mean	10.43	6.88	5.53

*Source: U.S. EPA, 1985a

3.3. INHALATION

The major anthropogenic carbon disulfide emission source is from viscose rayon manufacturing sites, but the largest global source of emissions is from natural sources (Khalil and Rasmussen, 1984). Sources of carbon disulfide emissions are fish processing (Hoshika et al., 1975), petroleum and starch manufacturing, plastics and refuse combustion, rubber abrasion (Graedel, 1978) and natural sources such as animal waste (Beard and Guenzi, 1983), decay of animal and plant tissue, volcanoes (Aneja et al., 1982), natural gas (Graedel, 1978) and biogenic emmissions from soils, oceans and salt marshes (Steudler and Peterson, 1984; Farwell et al., 1979; Adams et al., 1979; Lovelock, 1974; Aneja et al., 1982). Biogenic sulfur emmissions originate from anaerobic and aerobic bacterial reduction of sulfur compounds (Aneja et al., 1982).

Brodzinsky and Singh (1982) measured carbon disulfide in the air at rural/remote sites (61 samples) and urban/suburban sites (88 samples) in the United States; average concentrations were 41 and 65 ppt carbon disulfide, respectively. Assuming an average intake of 20 m^3 air/day, the average daily intake of carbon disulfide through inhalation is 2.6×10^{-3} mg in rural areas and 4.1×10^{-3} mg in urban areas. Jarke et al. (1981) qualitatively identified carbon disulfide in the ambient air in the Chicago area. Sandalls and Penkett (1977) measured carbon disulfide levels of 0.07-0.37 ppb in the ambient air of Harwell, England, and Ioffe et al. (1977) detected carbon disulfide at unspecified levels in ambient air of Leningrad, Russia. Khalil and Rasmussen (1984) estimated emissions of carbon disulfide in the northern hemisphere to be 0.3, 0.64, 0.05, 0.01, 0.26, 0.07 Tg/year (1 $Tg = 10^{12}$ g) from oceans, soils, marshes, volcanoes, chemical industries

and sulfur recovery, respectively. Waste gases from cellophane manufacturing processes contained 190-830 ppm carbon disulfide and the reported emmission factor was 67.5 m^3/ton of cellophane manufactured (Umemura et al., 1979). Off-gases from two different shale retorting processes emitted 4-31 ppm carbon disulfide (Sklarew et al., 1984). Adams (1979) measured average carbon disulfide emissions of 0.003-0.017 g S/m^2-year from flue gas desulfurization sludge ponds at two coal-fired, electric power generating plants in Alabama and Kentucky. Emissions from oceans, inland nonswamp soils and salt marshes were reported to be 0.0083, 0.0232 and 0.18 g S/m^2-year, respectively (Steudler and Peterson, 1984).

At viscose rayon manufacturing plants, exposure levels of carbon disulfide were $\geq$16 mg/m^3 (Westburg et al., 1984), and background levels of 8-13.1 ppm were reported (Cicolella and Vincent, 1984). Analysis of air inside a refinery revealed 0-0.09 mg carbon disulfide/m^3 air (Sarteur and Fayard, 1975).

3.4. DERMAL EXPOSURE

Pertinent data regarding dermal exposure to carbon disulfide could not be located in the available literature; however, carbon disulfide is a fumigant and exposure may occur during application.

3.5. SUMMARY

The U.S. EPA (1985a) monitored carbon disulfide in whole water, water and sediment samples. Carbon disulfide has been detected in lake, river, ocean and stagnant bay waters, and sea sediments (Kaiser et al., 1983; Lovelock, 1974). Carbon disulfide was also qualitatively identified in drinking waters of three cities and in sewage treatment plant effluents (U.S. EPA, 1974, 1975, 1980).

Carbon disulfide has been found in mother's milk (Pellizzari et al., 1982; Cai and Bao, 1981). Cai and Bao (1981) quantified the amount of carbon disulfide in the mother's milk of employees in rayon factories. Carbon disulfide has also been detected in grains fumigated with the compound (McMahon, 1971; Alumot and Bielorai, 1969).

The major anthropogenic source of carbon disulfide emmission is from viscose rayon manufacturing sites (U.S. EPA, 1980), but the largest global source of atmospheric emmissions is from natural sources (Khalil and Rasmussen, 1984). Carbon disulfide is emitted from a wide variety of manmade and natural sources (Hoshika et al., 1975; Graedel, 1978; Beard and Guenzi, 1983; Aneja et al., 1982; Steudler and Peterson, 1984; Farwell et al., 1979; Adams et al., 1979; Lovelock, 1974).

Carbon disulfide has been identified in the ambient air of rural and urban sites in the United States, in Chicago, IL, Harwell, England and Leningrad, Russia (Brodzinsky and Singh, 1982; Jarke et al., 1981; Sandalls and Penkett, 1977; Ioffe et al., 1977). Based on average atmospheric concentrations in rural and urban areas (Brodzinsky and Singh, 1982) the average daily intakes of carbon disulfide by inhalation are estimated to be 2.6×10^{-3} and 4.1×10^{-3} mg, respectively. Concentrations of this compound evolving from a cellophane manufacturing plant, shale-retort processes, power plant sludge ponds, oceans, soils and salt marshes have been measured (Umemura et al., 1979; Sklarew et al., 1984; Adams, 1979; Steudler and Peterson, 1984). The average ambient concentrations of carbon disulfide in U.S. urban/suburban and remote/rural areas are 65 and 41 ppt, respectively (Brodzinsky and Singh, 1982).

Pertinent data regarding dermal exposure could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

Pertinent data regarding the pharmacokinetics of ingested carbon disulfide could not be located in the available literature as cited in the Appendix.

4.1. ABSORPTION

In humans, carbon disulfide is absorbed substantially from the lungs. Herrmann et al. (1982) reported that volunteers exposed to 6-15, 27-40 or 89-108 mg carbon disulfide/m³ for 30 minutes retained an average of 52.4% of the inhaled chemical in the lungs (retention was 48.7% during the last 5 minutes of exposure). Beauchamp et al. (1983) reported that pulmonary retention of carbon disulfide is constant at ~70-80% initially for a wide range of exposures, declining to 15-45% at steady-state. Steady-state between inhaled and exhaled carbon disulfide is achieved within 1-2 hours of exposure (Beauchamp et al., 1983; WHO, 1981). Furthermore, less carbon disulfide is retained in the lungs of people exposed repeatedly than in those exposed to carbon disulfide for the first time (Beauchamp et al., 1983; WHO, 1981).

Pulmonary absorption of carbon disulfide in animals is similar to that in humans. McKenna and DiStefano (1977) administered 2 mg carbon disulfide/ℓ to anesthetized rats by tracheal cannula. The appearance of carbon disulfide in the blood obeyed first-order kinetics, with a $t_{1/2}$ of 19.3 minutes; steady-state in the blood was achieved within 90 minutes. In another study using rats (unanesthetized) exposed by inhalation to carbon disulfide (400 ppm), a steady-state concentration of carbon disulfide was achieved in the blood after 1 hour of exposure (Freundt and Schnapp, 1970).

Toyama and Kusano (1953) reported that steady-state was achieved in the blood of rabbits exposed to 20-150 ppm carbon disulfide within 1.5-2 hours of exposure. Steady-state was reached within 0.5-1.75 hours in dogs exposed by inhalation to 25-60 ppm carbon disulfide (McKee et al., 1943).

4.2. DISTRIBUTION

McKenna and DiStefano (1977) administered carbon disulfide (2 mg/ℓ) for 2.5 hours to anesthetized rats by tracheal cannula. The compound was eliminated from the blood in a biphasic process with $t_{1/2}$ values of 6 and 83 minutes for the slow and rapid phases, respectively. In another experiment, McKenna and DiStefano (1977) exposed unanesthetized rats by inhalation to carbon disulfide (2 mg/ℓ) for 8 hours, and then monitored the elimination from the tissues of both free and acid-labile carbon disulfide (carbon disulfide that is liberated upon treatment of a sample with acid). Unidentified metabolites, which formed in a reaction between carbon disulfide and a nucleophile, are thought to be the source of acid-labile carbon disulfide (Soucek and Madlo, 1953). After an 8-hour exposure, free carbon disulfide was located primarily in the fat, adrenals, liver and blood (59.5, 52.4, 14.8 and 12.7 µg carbon disulfide/g tissue, respectively), but was also found in the kidneys, brain, muscle and heart (7.9, 4.9, 1.2 and 0.8 µg carbon disulfide/g tissue, respectively). Acid-labile carbon disulfide was found primarily in the adrenals (66.5 µg carbon disulfide/g tissue), but was also found in fat, liver, blood, kidneys, brain, muscle and heart (9.9, 9.8, 2.8, 8.9, 6.5, 2.3 and 5.9 µg carbon disulfide/mg tissue, respectively). After exposure, free carbon disulfide was eliminated rapidly from the heart (2 hours), brain (4-6 hours), fat (4-8 hours) and muscle (minutes), but apparently more slowly from the liver and kidney (still present after 8 hours). The authors suggested that the presence of free

carbon disulfide in liver and kidney tissue at 8 hours was probably the result of the biotransformation of acid-labile metabolites to free carbon disulfide in these tissues, rather than the retention of free carbon disulfide. Acid-labile carbon disulfide was eliminated rapidly from fat (1 hour) and muscle (2-3 hours) but slowly from the brain, heart, liver and kidney (still present within 8 hours after exposure). Elimination curves were not given for other tissues.

Using whole body autoradiography, Bergman et al. (1984) monitored the distribution of ^{35}S- and ^{14}C-labeled carbon disulfide in NMRI mice. Mice were exposed by inhalation for 10 minutes to a concentration of 750 ppm carbon disulfide. Low temperature and conventional autoradiography were used to monitor the distribution and retention of volatile (free) carbon disulfide and nonvolatile carbon disulfide (metabolites), respectively. Volatile carbon disulfide was present in body fat, blood, lungs, liver and kidneys up to 2 hours after exposure. Very little carbon disulfide was found in the brain. The distribution pattern of carbon disulfide metabolites depended upon whether ^{14}C or ^{35}S was monitored. ^{35}S-metabolites were located in the liver, lung, kidneys and blood immediately after exposure, and were then concentrated in the liver and kidney 4 hours after exposure. The appearance of ^{35}S in cartilage and bone and the mucus gland of the pharynx (from 30 minutes to 48 hours after exposure) was thought to represent metabolic incorporation of sulfur, which resulted from metabolism of carbon disulfide. Elimination of ^{35}S-metabolites from the body (in urine and bile) occurred from 30 minutes to 24 hours after exposure. Immediately after exposure, ^{14}C-metabolites were found in the liver and kidneys (high concentrations), nasal mucosa, bronchi, adrenals, pancreas, thyroid and testes (especially seminiferous tubules); however, significant

decreases in the level of ^{14}C-metabolites were observed in the adrenal cortex, pancreas and testes within 1 hour after exposure. Marked retention of ^{14}C-metabolites was observed in the liver and thyroid (up to 48 hours after exposure). The kidney cortex, nasal mucosa and bronchi also retained large amounts of ^{14}C at 48 hours after exposure. Excretion of ^{14}C-metabolites in bile and urine was observed up to 24 hours after exposure.

In inhalation autoradiography studies similar to those conducted by Bergman et al. (1984), Danielsson et al. (1984) administered either ^{35}S-carbon disulfide of ^{14}C-carbon disulfide (750 ppm for 10 minutes) to pregnant C57Bl mice during different stages of gestation. Carbon disulfide and its metabolites crossed the placenta at all stages of gestation. Carbon disulfide was found to accumulate in embryonic cerebrospinal fluid during the middle and late phases of gestation. Metabolites of carbon disulfide were found in the neuroepithelium, bone and liver of the developing fetus throughout gestation.

4.3. METABOLISM

Numerous in vitro and in vivo experiments, involving animals and humans, have indicated that carbon disulfide is metabolized by two major pathways: by reaction with amino acids or reduced glutathione to form thiocarbamates or conjugated glutathione; and reaction catalyzed by cytochrome P450 to form reactive sulfur (Beauchamp et al., 1983; Neal, 1985).

4.3.1. Reaction with Amino Acids or Reduced Glutathione. The following compounds were isolated in the urine of workers exposed to carbon disulfide: thiourea, 2-thio-5-thiazolidinone (also called 2-mercapto-thiazolin-2-one-5), thiocarbamide (Pergal et al., 1972a,b) and 2-thiothiazolidine-4-carboxylic acid (Van Doorn et al., 1981). To account for the presence of thiocarbamide, 2-thio-5-thiazolidinone and 2-thiothiazolidine-4-carboxylic

acid, Van Doorn et al. (1981) proposed that carbon disulfide could react with amino acids and reduced glutathione as shown in Figure 4-1. Consistent with this hypothesis is the observation that acid-labile carbon disulfide (carbon disulfide released upon treatment of metabolites with acid) can be liberated from the tissues and urine of rats following pulmonary exposure to carbon disulfide (McKenna and DiStefano, 1977). Metabolites that give rise to acid-labile carbon disulfide are thought to be formed when carbon disulfide reacts with a nucleophile (Soucek and Madlo, 1953). Dithiocarbamates and conjugated reduced glutathione derivatives would give rise to carbon disulfide upon treatment with acid, and the method of formation hypothesized by Van Doorn et al. (1981) is consistent with that of Soucek and Madlo (1953).

4.3.2. **Reaction with Cytochrome P450.** A proposed pathway for the metabolism of carbon disulfide by cytochrome P450 is summarized in Figure 4-2. The following account is taken from Beauchamp et al. (1983):

> Carbon disulfide is metabolized by cytochrome P450 to an unstable oxygen intermediate (reaction i). The intermediate may either spontaneously degrade to atomic sulfur and carbonyl sulfide (reaction ii) or undergo attack by water forming atomic sulfur and monothiocarbonate (reaction iii). The atomic sulfur generated in these reactions may either covalently bind to macromolecules (reaction iv) or be oxidized to nonvolatile products such as sulfate (reaction v). The carbonyl sulfide formed in reaction ii may be converted to monothiocarbonate by carbonic anhydrase (reaction viii). Monothiocarbonate or its resonance form may further spontaneously degrade in reaction ix regenerating carbonyl sulfide or forming carbon dioxide and SH^- (reaction vii). The SH^- formed in reaction vii can subsequently be oxidized to sulfate or other nonvolatile metabolites (reaction vi).

Chengelis and Neal (1981) also proposed a mechanism to explain the appearance of thiourea in the urine of workers exposed to carbon disulfide. In the first step of urea synthesis, carbamoyl phosphate synthetase catalyzes a reaction with ATP, CO_2, NH_3 and H_2O to form carbamoyl phosphate.

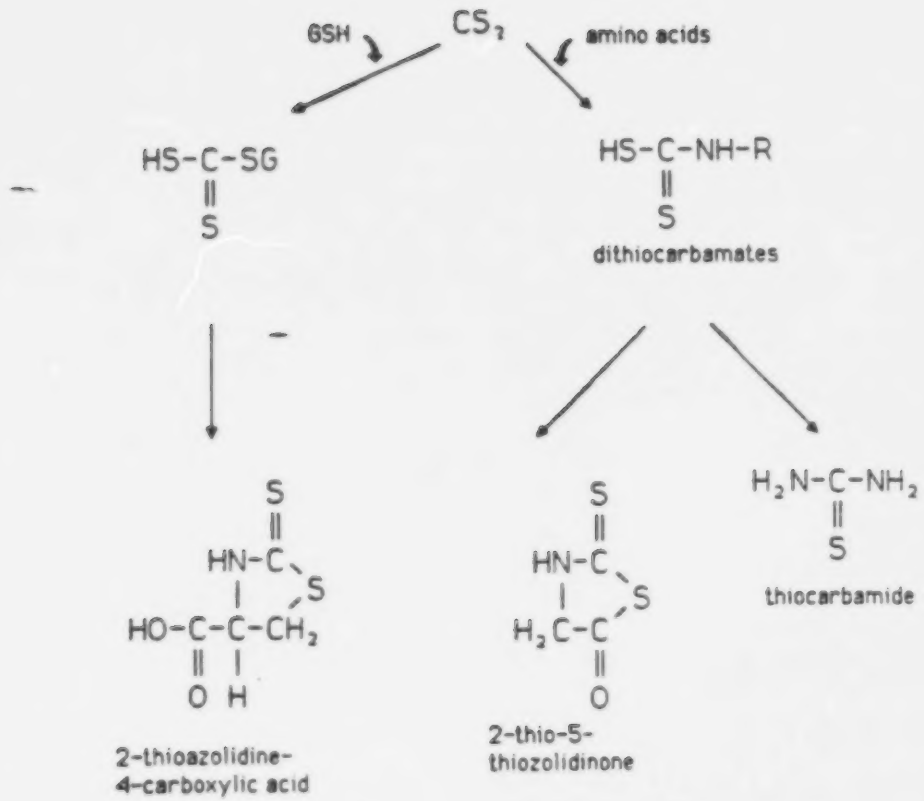

FIGURE 4-1

Metabolic Pathways

Source: Van Doorn et al., 1981

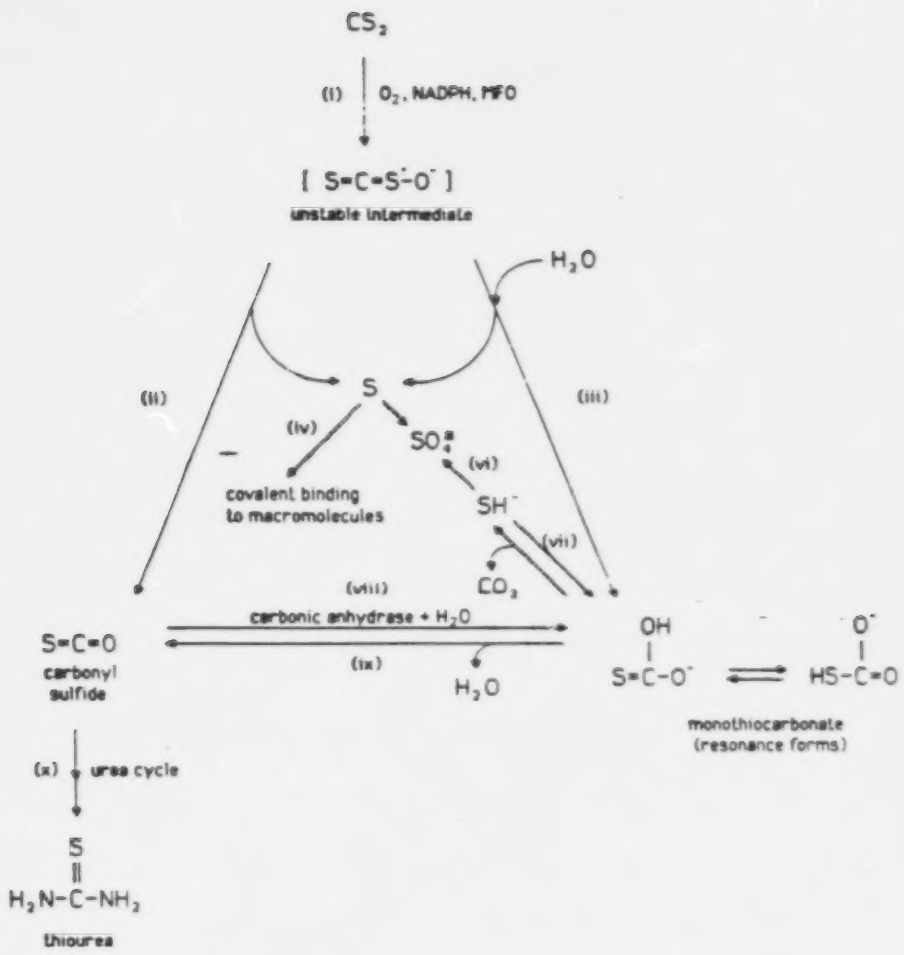

FIGURE 4-2

Metabolism of Carbon Disulfide via Cytochrome P450

Source: Beauchamp et al., 1983; Chengelis and Neal, 1981

Carbamoyl phosphate then enters the urea cycle, which ultimately liberates urea (Lehninger, 1978). Chengelis and Neal (1981) suggested that either carbonyl sulfide or monothiocarbonate can substitute for CO_2 in the reaction catalyzed by carbamoyl phosphate synthetase to form thiocarbamoyl phosphate. Thiocarbamoyl phosphate in turn enters the urea cycle in place of carbamoyl phosphate, which ultimately leads to the production of thiourea instead of urea.

4.4. EXCRETION

Inhaled carbon disulfide is excreted in expired air, urine and milk. In humans, 10-30% of the absorbed carbon disulfide is excreted unchanged in expired air (Soucek, 1957; McKee et al., 1943; Demus, 1964) and <1% is excreted unchanged in the urine (Soucek, 1957; Soucek and Pavelkova, 1953; McKee et al., 1943). The remainder of the absorbed compound is excreted primarily as metabolites in the urine (Beauchamp et al., 1983). Soucek and Pavelkova (1953) reported that pulmonary excretion of free carbon disulfide is a triphasic process requiring up to 97 hours for completion. Demus (1957, 1964, 1967) reported that urinary excretion of free carbon disulfide is proportional to exposure concentration; however, others have suggested that only high levels of exposure are correlated accurately with urinary carbon disulfide measurements (Djuric, 1967; Milic, 1965; Samcevic, 1965; Teisinger, 1961). Cai and Bao (1981) reported finding carbon disulfide in the milk of mothers exposed occupationally to carbon disulfide.

Anesthetized dogs exposed by inhalation to 25-60 ppm carbon disulfide for 0.5-1.75 hours (steady-state in blood) excreted 8-13% of the absorbed chemical through the lungs and 0.5% through the kidneys in 2.5-6.25 hours, the postexposure time required to desaturate the blood (McKee et al., 1943).

Rabbits exposed similarly to carbon disulfide (20-150 ppm) excreted 15-30% of the absorbed carbon disulfide through the lungs and 0.1% through the kidneys (Toyama and Kusano, 1953). Further information was not available in the secondary source from which these data were taken. In anesthetized rats exposed by inhalation to 2 mg/ℓ carbon disulfide for 2 hours, McKenna and DiStefano (1977) reported that elimination of free carbon disulfide in expired air was a single first-order process with a $t_{1/2}$ of 85 minutes. Magos et al. (1974) reported a $t_{1/2}$ of 35 minutes for pulmonary excretion of carbon disulfide in unanesthetized rats. In unanesthetized rats exposed by inhalation to 2 mg/ℓ carbon disulfide for 8 hours, excretion of bivalent sulfur metabolites in the urine was reduced to control levels within 12-14 hours after exposure was terminated (McKenna and DiStefano, 1977). Thus, McKenna and DiStefano (1977) concluded that free carbon disulfide is eliminated primarily from the lungs, while acid-labile carbon disulfide is eliminated primarily, and more slowly, in the urine.

4.5. SUMMARY

Pertinent data regarding the pharmacokinetics of ingested carbon disulfide could not be located in the available literature as cited in the Appendix.

In humans and animals, carbon disulfide is absorbed extensively from the lungs; steady-state between inhaled and exhaled carbon disulfide is achieved within 1-2 hours of exposure (Beauchamp et al., 1983; WHO, 1981; McKenna and DiStefano, 1977; Freundt and Schnapp, 1970; Toyama and Kusano, 1953; McKee et al., 1943). Studies on rats and mice (McKenna and DiStefano, 1977; Bergman et al., 1984) indicate that both unchanged carbon disulfide and its metabolites are distributed rapidly to body fat and highly perfused tissues.

Free carbon disulfide is eliminated more rapidly from the tissues than are its metabolites (McKenna and DiStefano, 1977). Neither free carbon disulfide nor its metabolites appear to bioaccumulate in any tissue. Danielsson et al. (1984) also showed that carbon disulfide and its metabolites can cross the placenta throughout gestation, with metabolites accumulating in the bone, liver and neuroepithelium of the fetus.

Numerous *in vitro* and *in vivo* studies on animals and humans have suggested that carbon disulfide is metabolized by two major routes: by reaction with amino acids or reduced glutathione to form thiocarbamates or conjugated glutathione, and by reactions catalyzed by cytochrome P450 to form reactive sulfur (McKenna and DiStefano, 1977; Van Doorn et al., 1981; Soucek and Madlo, 1953; Chengelis and Neal, 1980, 1981; Bond and DeMatteis, 1969; Freundt and Dreher, 1969; Hunter and Neal, 1975; Freundt and Kuttner, 1969; Freundt et al., 1976; Mack et al., 1974; DeMatteis and Seawright, 1973; Dalvi et al., 1974, 1975; Dalvi and Neal, 1978; DeMatteis, 1974; Catignani and Neal, 1975), which may further react to form thiourea, carbonyl sulfide or monothiocarbonate (Beauchamp et al., 1983).

Inhaled carbon disulfide is rapidly excreted in expired air, urine and milk. Unchanged carbon disulfide is eliminated primarily through the lungs (10-30% of absorbed carbon disulfide) and secondarily through urine (<1%), while its metabolites (70-90% of absorbed carbon disulfide) are eliminated more slowly and principally through the urine (McKenna and DiStefano, 1977; Soucek, 1957; McKee et al., 1943; Demus, 1964; Soucek and Pavelkova, 1953; Cai and Bao, 1981; Toyama and Kusano, 1953; Bergman et al., 1984). In humans, pulmonary excretion of carbon disulfide is reported to be a triphasic process that requires up to 97 hours for completion (Soucek and Pavelkova, 1953). In anesthetized rats, pulmonary excretion was a single

first-order process with a $t_{1/2}$ of 85 minutes. Magos et al. (1974) reported a $t_{1/2}$ of 35 minutes for pulmonary excretion of carbon disulfide in unanesthetized rats. In unanesthetized rats, excretion of bivalent sulfur metabolites in the urine was reduced to control levels within 12-14 hours of exposure (McKenna and DiStefano, 1977).

5. EFFECTS

5.1. CARCINOGENITICY

Evidence that occupational exposure to carbon disulfide may be carcinogenic is largely negative.

In a case-control study, Checkoway et al. (1984) and Wilcosky et al. (1984) reported an association between lymphocytic leukemia and multiple solvent exposure. The cases selected for analysis consisted of 11 male hourly workers from the U.S. rubber industry whose deaths were attributed to lymphocytic leukemia. Controls were composed of a 20% age-stratified random sample (1280 whites and 70 blacks) taken from a cohort identified in another study (McMichael et al., 1976). Exposure histories were reconstructed from plant records. Odds ratios and chi-square tests of significance were conducted according to methods described by Mantel and Haenszel (1959). Of the 24 solvents to which workers were exposed (levels not reported), carbon disulfide and carbon tetrachloride were shown to have the strongest association with leukemia [for carbon disulfide, the number of cases exposed was 7, the odds ratio was 8.7 and the chi-square value was 12.82 ($p<0.001$)].

In this study, there was no association between exposure to carbon disulfide and any other types of cancer (Wilcosky et al., 1984). Furthermore, Wilcosky et al. (1984) pointed out that given the large number of solvents and cancers examined, the finding of a positive association between cancer and exposure requires "cautious interpretation." When large numbers of variables are simultaneously examined for association, finding a positive association based on statistical methods is highly probable, and the interpretation of the apparent association of occupational exposure to carbon disulfide with leukemia is unclear.

In a 15-year prospective follow-up study on viscose rayon workers, Nurminen and Hernberg (1984) reported that there was no association between occupational exposure to carbon disulfide and cancer mortality. The exposed and control cohorts consisted of 343 viscose rayon workers and 343 paper mill workers, respectively. Mortality that was due to lung cancer was lower among viscose rayon workers (4/4685 man-years) than among controls (9/4830 man-years), but the mortality rate ratio (0.46) was not statistically significant. There were 10 deaths from "other neoplasms" (ICD codes A45-A50, A52-61) in each cohort. When compared with Finnish national mortality rates in 1975 set as a standard of 100, relative mortality from lung cancer among viscose rayon workers was 74 while that among paper mill workers (controls) was 154. These values were not statistically different from the "general standard."

Oncogenicity bioassays have not been conducted in animals and carbon disulfide has not been scheduled for chronic bioassay by the NTP (1985).

5.2. MUTAGENICITY

Mutagenicity studies with carbon disulfide have yielded primarily negative results. Carbon disulfide was not mutagenic in the following bacterial reverse mutation assays: Salmonella typhimurium strain TA100 with or without S-9 (0.63-3.15 µg/plate in suspension for 1 hour or 8400 ppm gas over plate for 48 hours) (Hedenstedt et al., 1979); S. typhimurium strains TA98, TA100 with or without S-9 (300-1000 µM/plate) (Donner et al., 1981); S. typhimurium strains TA98, TA100, TA1535, TA1537 with or without S-9 (33.3-3333.3 and 20.7-2070 µg/plate in a preincubation test) (Haworth et al., 1983); and in Escherichia coli strain WP2uvrA with or without S-9 (20-600 µM/plate) (Donner et al., 1981). Negative results were also reported in sex-linked recessive lethal studies in Drosophila melanogaster

(200-800 ppm for 24 hours; 20 and 40 ppm for 7 hours) (Donner et al., 1981; Belliles et al., 1980) and in bone marrow cytogenesis and in dominant-lethal studies in rats (20-40 ppm acutely for 7 hours or subacutely for 5 daily exposures of 7 hours each) (Belliles et al., 1980).

Belliles et al. (1980) reported weakly positive responses in a host-mediated assay that used CD-1 mice and S. typhimurium strain TA98 in an unscheduled DNA synthesis using WI-38 human fibroblasts. These results are of dubious value. In the UDS test, the positive control (benzo[a]pyrene) failed to yield a clear positive response. In the host-mediated assay, a low survival was found in the treated group; thus the positive result, because of clumping or differential cell growth, could be spurious. Beauchamp et al. (1983) mentioned that reports of genotoxicity have appeared in the foreign literature, but the lack of details precludes interpretation of these studies.

5.3. TERATOGENICITY

Jones-Price et al. (1984a,b) conducted oral teratology studies on CD rats and New Zealand White rabbits. Groups of 22-27 pregnant CD rats were treated by gavage with 0, 100, 200, 400 or 600 mg carbon disulfide/kg/day in corn oil on days 6-15 of gestation and were sacrificed on day 20 of gestation (Jones-Price et al., 1984a). Maternal endpoints monitored were clinical signs of toxicity, body weight, mortality, liver weight, gravid uterine weight, number of implantations and numbers of live, dead and resorbed fetuses. All fetuses were weighed and examined for external, skeletal and visceral malformations. Clinical signs of maternal toxicity were observed in all carbon disulfide-treated dams, with the most severe effects observed at 400 and 600 mg/kg/day. These effects included abnormal posture, rigidity or paralysis of hindlimbs, ataxia, lethargy and rough or erect coat. During

treatment and throughout gestation, a significant ($p<0.01$, William's test; $p<0.05$, Dunnett's test) dose-related reduction in maternal weight gain occurred compared with controls at 200, 400 and 600 mg/kg/day (during treatment only) or at 400 and 600 mg/kg/day (during gestation). Maternal relative liver weights were elevated significantly at 400 and 600 mg/kg/day. There were no compound-related effects on gravid uterine weight, number of implants/litter, proportion of litters with dead, resorbed or affected fetuses, percent resorbed, dead or affected fetuses/litter, number of live fetuses/live litter and percent males/live litter. There was a dose-related decrease in average fetal body weight/litter; significant decreases were observed at 200, 400 and 600 mg/kg/day ($p<0.05$, Dunnett's test; $p<0.01$, William's test). Although a small percentage of malformed fetuses was observed at all exposure levels, there was no clear dose response pattern. The percentage of malformed fetuses/litter was 5.04 ± 1.62, 1.51 ± 0.86, 6.88 ± 2.75, 2.54 ± 1.44 and 0.53 ± 0.37 for the vehicle control, 100, 200, 400 or 600 mg/kg/day groups, respectively. Four of the malformed fetuses had branched rib (100 mg/kg/day), micromelia (200 mg/kg/day), constricted tail (200 mg/kg/day), and fused kidneys, displaced ovaries and missing adrenals (400 mg/kg/day), malformations not commonly observed among historical controls. The investigators concluded that exposure to carbon disulfide did not increase the incidence of fetal malformations in this study.

Groups of 23-28 pregnant New Zealand White rabbits were treated by gavage with 0, 25, 75 or 150 mg carbon disulfide/kg/day in corn oil on days 6-19 of gestation and were killed on day 30 of gestation (Jones-Price et al., 1984b). Maternal and fetal endpoints examined were identical to those in the Jones-Price et al. (1984a) study in rats. Maternal toxicity (decreased body weight during treatment and gestation, decreased gravid uterine

weight, increased absolute and relative liver weight) was dose-related but only significant ($p<0.01$, William's test; $p<0.05$ Dunnett's test) at 75 and 150 mg/kg/day. Fetal effects included a dose-related and statistically significant (all doses, $p<0.05$, Fisher's Exact test) increase in percent resorptions/litter (12.3, 32.4, 41.6 and 61.16% for 0-150 mg/kg/day, respectively), and a dose-related increase in percent fetal malformations/litter that was significant only at 150 mg/kg/day (19.51% high dose vs. 5.72% control; $p<0.05$, Dunnett's test). The malformations observed were those commonly observed among historical controls. A significantly increased number of resorptions/litter in rabbits at a level where no maternal toxicity was observed (25 mg/kg/day) suggests that ingested carbon disulfide may have a primary effect on the developing fetus.

Inhalation studies show that carbon disulfide may be teratogenic in rats, although the data are equivocal (Table 5-1). The highest inhalation exposure level used was 2000 mg/m^3. In a paper by Yaroslavskii (1969), albino mice (15-20/group) and Wistar rats (12-14/group) were exposed to 2000 mg/m^3 for 2 hours daily throughout pregnancy; in addition, half the mice were exposed for 2 weeks before mating. No indication was given as to how control animals were housed during gestation. Some animals were allowed to deliver their young while in others the fetuses were removed on the 19th or 20th day of gestation. In the first of two experiments using rats, the average number of embryos implanting and the number of live fetuses was significantly decreased below control values. In the second experiment, the number of embryos dying before implantation was significantly increased while the number of implantations was reduced but not significantly. No effect was seen on fetal weight. The percent of live fetuses based on number of corpora lutea was also significantly reduced. Thus, while the

TABLE 5-1

Teratogenicity Testing of Carbon Disulfide by Inhalation

Species/Strain	Number of Dams at Start	Daily Dose or Exposure	Treatment Days	Observation Days	Maternal Response	Fetal Response	Reference
Rat/Sprague-Dawley or Wistar	~30/group	0, 20 or 40 ppm for 6 or 7 hours/day	days 1-19 of gestation; 1 generation only	day 21	NR	No embryotoxicity or grossly visible terata	Hardin et al., 1981
Rat/Sprague-Dawley	10/group	0, 300, 600 ppm for 6 hours/day	days 6-15 of gestation	day 21	no effect	No embryotoxicity or grossly visible terata. Delayed ossification of sternum observed in 300 ppm exposed fetuses (non-significant)	Choudhury and Manson, 1981
Rat/"mongrel"	NR	0, 0.7 or 4.2 ppm	all of gestation; 1 generation only	NR	NR	4.2 ppm: "slight embryotoxicity" 0.7 ppm: no effect	Salnikova and Chirkova, 1974
Rat/Wistar	32/group	0, 50, 100 or 200 mg/m³ (0, 16, 32 or 64 ppm) for 8 hours/day	all of gestation; 1 generation only	at term and during post-natal period; 2 generations	NR	F_1 generation: 50 mg/m³: no teratogenic or embryotoxic effects; behavioral deviations of questionable significance (increased "emotional activity" and reduced exploratory activity) 100-200 mg/m³: increased preimplantational loss; increased malformations (hydrocephalus; club foot); decreased fetal body weight, behavioral deviations and mild effects on liver, brain and kidney F_2 generation: behavioral deviations at all levels; terata (as in F_1) at 50 and 100 mg/m³; no embryotoxicity	Tabacova et al., 1978
Rat/NR	NR	0.1 or 3.2 ppm (0.3 or 10 mg/m³)	NR	postnatal period	NR	Behavioral abnormalities (retarded sensory development and learning) at 3.2 but not at 0.1 ppm	Tabacova and Hinkova, 1976, 1979

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TABLE 5-1 (cont.)

Species/Strain	Number of Dams at Start	Daily Dose or Exposure	Treatment Days	Observation Days	Maternal Response	Fetal Response	Reference
Rat/albino NOS	30-32/group	0, 0.03, 10, 100 or 200 mg/m³ (0, 0.0096, 3.2, 32 or 64 ppm) for 8 hours/day	all of gestation; 2 generations	at term and during post-natal period; 2 generations	positive response in F_0 at 200 mg/m³ and in F_1 at 10, 100 and 200 mg/m³	F_1 generation: congenital malformations (hydrocephalus, clubfoot, tail deformation) at 100 and 200 mg/m³; effects on nervous system at 0.03 and 10 mg/m³ in postnatal period (higher doses not examined) F_2 generation: congenital malformations of greater incidence and severity than in F_1 at all levels of exposure (hydrocephalus, micro-encephaly, club foot, tail deformation, hypognathia, generalized edema); effects on nervous system at 0.03-10 mg/m³ (higher doses not tested); significant changes in lipid metabolism at 200 mg/m³	Tabacova et al., 1983
Rat/Wistar	12-14/group	0 or 2000 mg/m³ (642 ppm) 2 hours/day	all of gestation	day 19-20 of gestation; 1 generation only	NR	Increased pre- and postimplantational loss; no malformations (terata were not specifically sought)	Yaroslavskii, 1969
Mouse/NR	15-21/group	0 or 2000 mg/m³ (642 ppm) 2 hours/day	all of gestation	day 19-20 of gestation; 1 generation only	NR	Increased pre- and postimplantational loss; no malformations	Yaroslavskii, 1969
Rabbit/New Zealand White	15-20/group	0, 20, 40 ppm for 6 or 7 hours/day	days 1-24 of gestation	day 30 of gestation; 1 generation only	NR	No embryotoxicity or grossly visible terata	Hardin et al., 1981

NR = Not reported; NOS = not otherwise stated

endpoints that were statistically significant differed between the two experiments, the tendency for increased preimplantation loss and a slight rise in postimplantation loss was evident in both experiments. In mice, premating exposure did not affect the number of corpora lutea, but preimplantation loss was significantly higher than in the controls, and the number of live fetuses was also significantly reduced. Thus, both preimplantation and postimplantation loss were increased with CS_2 exposure. The authors also reviewed information relating to the effects of CS_2 on inhibiting monoamine oxidase, which results in a buildup of serotonin levels. In an effort to further increase the levels of serotonin, the serotonin precursor tryptophan was injected (500 mg/kg, 1st to 19th or 20th day of pregnancy) with or without CS_2 exposure. The incidence of preimplantation loss was further increased (and the number of implanted embryos was further decreased) with the combination of tryptophan plus CS_2 versus CS_2 alone. The number of live fetuses was also further reduced but was probably not significantly different from CS_2 alone. Tryptophan alone had no significant effect on any endpoint. No information was given on maternal toxicity or on teratogenesis in either rats or mice.

In a study by Hardin et al. (1981) female CD rats and New Zealand white rabbits were exposed to 0 (filtered air), 20 or 40 ppm (60 or 120 mg/m^3) CS_2 by inhalation. Half the animals were exposed before mating (7 hours/day, 5 days/week for 3 weeks). Following pregestational exposure, animals were mated to unexposed males and exposed to the same concentrations of CS_2 on days 0-18 or 6-18 (rats) or on days 0-21 or 7-21 (rabbits). Rats were killed on day 20 of gesatation, rabbits on day 30, and maternal organs and uterine contents were examined. Maternal animals showed no changes in organ appearance or weight related to CS_2 exposure. There were no effects

noted in terms of the number of corpora lutea, implantations, resorptions, dead or live fetuses per litter, fetal weight, crown-rump length, sex ratio or abnormalities following CS_2 exposure. Scattered malformations were observed, but were unrelated to exposure level. There was a high incidence of mortality in rabbits exposed pregestationally and either 0-18 or 6-18 days of gestation to 20 ppm CS_2; however, the incidence in the groups similarly exposed to 40 ppm was no greater than controls. Additionally, rats in this study had an outbreak of Sialodacryoadenitis during the acclimatization period. Despite these incidental problems, the histopathological examinations at terminal sacrifice did not reveal an underlying disease state; deaths appeared unrelated to CS_2 exposure.

Choudhury and Hanson (1981) also observed no evidence of embryotoxicity or grossly visible malformations in Sprague-Dawley rats exposed to 300 or 600 ppm carbon disulfide for 6 hours/day on days 6-15 of gestation. Pregnant rats in this study were fed a semisynthetic diet containing adequate levels of nutrients, as recommended by the American Institute of Nutrition (1977), to support growth, maintenance and gestation. A careful and detailed examination of fetuses for terata, and analysis of essential trace metal concentrations in the body of fetuses were performed to determine the mechanism of carbon disulfide toxicity in pregnant rats and their neonates. The results of these studies indicated a marked increase in the incidence of delayed ossification of the sternum of fetuses exposed to 300 ppm of carbon disulfide. However, this incidence is reversible and considered as developmental delay. Adverse effects other than delayed ossifications, observed in fetuses exposed to 300 ppm carbon disulfide, were unremarkable in both rat dams and fetuses exposed to either 300 or 600 ppm carbon disulfide.

Adverse effects on the fetus at markedly lower levels were reported only by investigators from Eastern bloc countries. Salnikova and Chirkova (1974) observed "slight embryotoxicity" in rats exposed to 4.2, but not 0.7 ppm throughout gestation. The daily exposure schedule was not reported and it is impossible to further interpret these results. Studies in rats by Tabacova et al. (1978), Tabacova and Hinkova (1976, 1979) and Tabacova et al. (1983) indicate that terata are associated with concentrations of carbon disulfide below the TLV for this chemical. The study by Tabacova et al. (1983) demonstrates that teratogenic effects appear at lower doses and with increasing severity in successive generations of exposed animals.

The Tabacova et al. (1983) study yields the lowest level of exposure to carbon disulfide (0.03 mg/m³) at which adverse effects were seen. In this study, female albino rats were exposed by inhalation to 0, 0.03, 10, 100 or 200 mg carbon disulfide/m³ for 8 hours/day throughout gestation (21 days). Some were allowed to deliver naturally and others were subjected to Caesarean section. The surviving F_1 rats were reared to maturity and allowed to mate. Half of the pregnant F_1 rats were exposed similarly to carbon disulfide during the entire period of gestation and half were not. Indices of maternal toxicity and pre- and postnatal development were evaluated for all generations. Indices of maternal toxicity included maternal weight gain during gestation, oxygen consumption of the placenta, free fatty acids in the liver at term, lipid peroxides in the placenta at term, and levels of aminopyrine-N-demethylase and aniline hydroxylase in the liver at term. Indices of prenatal development included data on congenital malformations and lipid metabolism. Indices of postnatal development included hexobarbital sleeping time as a test for MFO function, and tests of motor coordination (crossing a narrow path and motor activity in an open field).

Maternal toxicity was observed in the F_0 generation at 200 mg/m³ and in the F_1 generation at 10, 100 and 200 mg/m³. Congenital malformations (hydrocephalus, club foot, tail deformation) were observed in the F_1 generation at 100 and 200 mg/m³. No malformations were observed in controls. In the F_2 generation, a dose-related increase in congenital malformations was seen in fetuses exposed in utero at all concentrations of carbon disulfide. None of the controls had malformations. Malformations in the F_2 rats included hydrocephalus, microcephaly, club foot, tail deformation, hypognathia and generalized edema. Both the incidence and the severity of malformations were greater in the F_2 than in the F_1 generation. Compared with controls, F_2 fetuses taken from dams exposed to 200 mg/m³ had significant changes in lipid metabolism (decreases in hepatic phospholipids to triglycerides). These changes were not observed in any of the F_1 or F_2 progeny. Motor coordination was impaired in both the F_1 and F_2 progeny exposed in utero to 10 mg/m³ (animals receiving higher doses were not tested), motor activity increased at both 0.03 and 10 mg/m³. The effects were more severe in the F_2 than in the F_1 progeny. Hexobarbital sleeping time was increased at ages 7 and 14 days in both F_1 and F_2 progeny exposed in utero to 10 mg carbon disulfide/m³. No effects on hexobarbital sleeping time were observed in progeny of either generation exposed in utero to 0.03 mg carbon disulfide/m³. Hexobarbital sleeping time was not tested in animals exposed to higher concentrations of carbon disulfide.

Tabacova et al. (1983) noted that prenatal inhalation exposure to carbon disulfide resulted in alterations of morphological and functional development of the fetus. Altered functional development, manifested as prolonged hexobarbital sleeping time (altered hepatic xenobiotic metabolizing ability)

at 10 mg/m³ and altered motor activity at 0.03 mg/m³ occurred in the F_1 offspring at lower levels than did morphological alterations (50 mg/m³). The observation that maternal toxicity occurred at 200 mg/m³ in the F_0 (naive) generation but at 10 mg/m³ in the F_1 (prenatally exposed) generations indicated that exposure to carbon disulfide at low levels during the prenatal period may sensitize the individual, resulting in lowered toxic thresholds later in life. The authors suggested carbon disulfide acts by interfering with the hormonal regulation of prenatal development, possibly resulting in permanent alteration of the xenobiotic metabolizing function of the body and impaired future ability to detoxify carbon disulfide. This phenomenon may also have been responsible for the occurrence of fetal malformations at 0.03 mg/m³ in the F_2 generation, while no fetal abnormalities occurred at 10 mg/m³ in the F_1 generation. Despite availability of enormous toxicological endpoints, Tabacova et al. (1983) did not provide information pertinent to experimental protocols, purity of the chemical or the compound studied and the type of diet used. The repeat generation Bulgarian study did not observe any incidences of terata in controls; however, in usual circumstances ~1% incidence of teratological events on an average have been reported in control populations.

5.4. OTHER REPRODUCTIVE EFFECTS

A number of rat studies and human occupational exposure studies suggest that inhaled carbon disulfide may disturb male copulatory behavior (Zenick et al., 1984a,b; Tepe and Zenick, 1984; Cirla et al., 1978; Lancrajan et al., 1969; Lancrajan, 1972), cause reductions in ejaculated sperm count (Lancranjan, 1972; Lancranjan et al., 1969; Tepe and Zenick, 1984; Zenick et al., 1984a,b). Other investigators reported no effects on sperm count or semen volume in occupationally exposed humans (Meyer, 1981) and no effects

on spermatogenesis or the spermatozoa (Salnikova and Chirkova, 1974) or the ultrastructural appearance of the seminiferous tubule (Gondzik, 1976) in rats.

In a study by Gondzik (1971), 9-15 "mongrel" rats per dose group were treated intraperitoneally with distilled CS_2 dissolved in peanut oil at a dose of 12.5 mg/kg every second day for 60 days. A peanut oil control group and an untreated control group were also run. In a second experiment, animals were treated with 25 mg/kg CS_2 every second day for 60 days with a concurrent vehicle control and untreated control group. In the third experiment, animals were treated the same way as in the second experiment except that treatment continued for 120 days. Animals were killed at the end of treatment and testes were examined histologically. No effect of CS_2 on the testis was seen in the first experiment (12.5 mg/kg bidaily for 60 days). In the second experiment (25 mg/kg bidaily for 60 days), the vascular wall in the testis was thickened and the vessels engorged with blood cells, the layers of seminiferous epithelium were disorganized and the number of spermatozoa in the tubular lumen were reduced. In the third experiment, testes of animals treated with 25 mg/kg CS_2 (120 days bidaily) showed advanced regressive lesions involving all parts of the structure of the testis, including folding and shrinking of the tubular basement membrane, scant stromal tissue and loss of spermatogonia. Spermatogenesis was absent but Sertoli cells were present in every tubule. The number of Leydig cells in the intertubular spaces was reduced and the cells showed signs of degenerative vacuolation. No information was given in this paper on the general toxicity of CS_2 in these animals and there was no follow-up on reversal of these effects although the authors suggested that the nature of the effects indicated their irreversibility.

An association between decreases in ejaculated sperm count and impaired copulatory dysfunction has been demonstrated (Tepe and Zenick, 1984; Zenick et al., 1984a,b) suggesting a CNS rather than a gonadal role for CS_2 in reproductive dysfunction. Other studies suggest that occupational exposure to carbon disulfide may decrease levels of plasma gonadotropins or testosterone (Lancrajan et al., 1969; Cirla et al., 1978; Maugeri et al., 1966), but others reported increases (Wägar et al., 1983) or no changes in these variables (Cirla and Graziano, 1981). The discrepancy between these reports may be due to an inability to accurately quantify levels of exposure, although several rat studies conducted by a single laboratory also reported contradictory results. Tepe and Zenick (1984) initially reported a significant decrease in plasma testosterone; however, in a more controlled study (Zenick et al., 1984a,b), endocrinologic changes were not observed in rats exposed to 600 ppm carbon disulfide for 10 weeks. No treatment-related effects were seen in either basal FSH, LH or testosterone levels or after stimulation with exogenous LH or HCG. Tabacova et al. (1978) reported that reproductive capacity was not affected in albino rats whose dams were exposed to up to 200 mg/m³ (64 ppm) carbon disulfide throughout gestation. However, alterations in menstrual cycle and increased rate of spontaneous abortion caused by inhaled CS_2 have been reported (Petrov, 1969; Vaszleva, 1973; Cai and Bao, 1981; Bezvershenko, 1965). Inhalation studies that attempted to quantify exposure are summarized in Table 5-2.

5.5. CHRONIC AND SUBCHRONIC EFFECTS

5.5.1. Oral Studies. Only two subchronic oral studies were located in the available literature. The studies demonstrate that repeated ingestion of carbon disulfide causes neurologic and hematologic damage. In order to examine the hematologic effects of carbon disulfide, Pilarska et al. (1973) administered carbon disulfide (25 mg/kg/day in arachis oil), presumably by

TABLE 5-2

Reproductive Toxicity of Inhaled Carbon Disulfide

Species/Sex	Exposure	Response	Reference
Human/M	13-26 ppm (occupational)	Disturbances in sexual dynamics; higher frequency of asthenuspermia, hypospermia and teratospermia	Lancrajan et al., 1969; Lancrajan, 1972
Human/M	<2, 2-10 and >10 ppm (occupational)	No effect on sperm count or semen volume	Meyer, 1981
Human/M	~19-77 ppm (60-240 mg/m³; occupational)	Reduction in sexual activities; reductions in FSH and LH (no dose-response relationship when individuals were divided into groups which seemingly reflected different levels of exposure)	Cirla et al., 1978
Human/F	12-18 ppm (37-56 mg/m³)	Menstrual disorders; greater incidence of toxemia in pregnancy	Cai and Bao, 1981
Human/F	9 ppm (28 mg/m³; occupational)	Increased number of spontaneous abortions	Petrov, 1969
Human/F	3 ppm (9.3 mg/m³)	Altered menstrual cycle	Vasileva, 1973
Rat/M (NOS)	0.74 or 3.33 ppm (2.3 or 10.4 mg/m³) for 6 months	No effects on spermatogenesis or spermatozoa	Salnikova and Chirkova, 1974
Rat/M (NOS)	426 ppm (1.3 mg/ℓ) for 12-18 weeks	No effects on seminiferous tubule ultrastructure	Gondzik, 1976
Rat/M/Long-Evans Hooded	600 ppm, 6 hours/day, 5 days/week for 10 weeks; mated at 1, 4, 7 and 10 weeks; killed at 10 weeks	Significant decreases in body weight (week 10), ejaculation latency (weeks 4, 7, 10), mount latency (week 10), ejaculated sperm count (weeks 7 and 10); no changes in testicular histology, endocrinology or epididymal sperm count	Zenick et al., 1984a,b
Rat/M/Long-Evans Hooded	350 or 600 ppm, 5 hours/day, 5 days/week for 10 weeks; killed at 10 weeks	No changes in reproductive organ weights or plasma gonadotropin levels; slightly lower epididymal sperm counts and significant lower levels of plasma testosterone at 600 ppm	Tepe and Zenick, 1984
Rat/M/Long-Evans Hooded	600 ppm, 5 hours/day, 5 days/week for 10 weeks; mated at 1, 4, 7 and 10 weeks; killed at 10 weeks	Significant decreases in mount latency (week 7 and 10), ejaculation latency (weeks 4, 7 and 10) ejaculated sperm count (weeks 7 and 10); significant but mild depression of plasma testosterone (week 1 only)	Tepe and Zenick, 1984
Rat/M,F/albino, NOS	16, 32 or 64 ppm (50, 100 or 200 mg/m³) *in utero* throughout gestation; no exposure after birth	No effect on reproductive capacity	Tabacova et al., 1978

NOS = Not otherwise specified

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gavage to 13 Wistar rats for 60 days. Controls consisted of 10 unexposed and 8 vehicle-exposed rats, respectively. Differences between controls and treated rats were statistically evaluated using the student's T-test (α=0.05). Carbon disulfide-exposed rats had normochromic and normocytic anemia, eosinopenia and reticulocytosis.

Dietzmann and Laas (1977) investigated the effects of ingested carbon disulfide on the CNS. Male Wistar rats (n=35, ~250 g) were treated by gavage with 0.06 mℓ carbon disulfide/rat twice weekly for 8 weeks and then twice weekly with 0.12 mℓ carbon disulfide/rat for an additional 12 weeks. Exposed rats were killed after 4, 8, 12, 16 and 20 weeks and a group of six controls was killed after 20 weeks. Tissues of the brain and spinal cord were examined histologically (light and electron microscopy) at the specified intervals. After 16 and 20 weeks of exposure, the parietal cortex was examined for enzymatic activity (monoamine oxidase, ATPase, glucose-6-phosphatase, acetylcholinesterase, succinic dehydrogenase, glutamic dehydrogenase and arylsulfatases). Clinical signs of toxicity observed during the first few weeks of exposure included disorientation and "reeling gait," which disappeared after 3 weeks of treatment. After 12 weeks of treatment, hair loss was observed, and after 16 weeks of treatment, paraplegia of the hind and forelimbs occurred in "several animals." Histological changes observed after 12 weeks included the following: destruction of ganglion cells in the cerebrum, cerebellum and brain stem; elective parenchymal necrosis in frontal and parietal cortices; "micro-maculated fresh hemorrhagic extravasates in the areas of nucleus ruber and pons"; and axonal swelling and destruction of the myelin sheath. The only enzymatic changes relative to controls were reported to occur after 20 weeks of exposure.

These included reductions in activities of succinic dehydrogenase and acetylcholinesterase, only in areas of elective parenchyma necrosis, and reductions in activities of arylsulfatases and glutamic dehydrogenase in the entire brain.

5.5.2. **Inhalation Studies.** Occupational exposure to carbon disulfide has been associated with cardiovascular, neurologic, immunologic and ocular effects. Animal inhalation studies have demonstrated that carbon disulfide can cause neurologic, cardiovascular, hepatic, renal, gastrointestinal and hematologic effects. Due to the large number of studies available, detailed reporting of each study is beyond the scope of this document. Instead, major studies, identified from several reviews (Beauchamp et al., 1983; U.S. EPA, 1983; NIOSH, 1978) and searches of the literature, will be discussed. Human studies that used controls and provided exposure data are summarized in Table 5-3. Animal studies are summarized in Table 5-4.

5.5.2.1. **NEUROLOGICAL EFFECTS** -- Case reports from the viscose rayon industry have suggested that exposure to carbon disulfide at 144-321 ppm may cause psychosis, polyneuritis (absent or weakened Achilles or patellar reflexes), tremors, weakness of limbs, myopathy and vertigo (Vigliani, 1954). Reports from the early literature suggest an association between insanity and exposure to carbon disulfide (NIOSH, 1978; Delpech, 1856; Viscose Rayon Survey, 1938; Peterson, 1892; Hamilton, 1915; Jump and Cruice, 1904; Francine, 1904).

Epidemiology studies suggest that occupational exposure to carbon disulfide is associated with psychological disorders (psychomotor, behavioral and intelligence tests) (Hanninen, 1971; Tuttle et al., 1976), but exposure levels were not adequately quantified in these studies. Other studies have shown electromyographic evidence (reduced motor and sensory nerve conduction

TABLE 5-3

Toxicity Summary for Occupational Exposure

General Type of Effect	Exposure	Response	Reference
Neurologic	<2 ppm	Reductions in conduction velocity of motor and slower motor fibers of ulnar nerve	Hirata et al., 1984
	1.0-7.6 ppm for average of 12.1±6.9 years	Reductions in aural sensory and peroneal motor nerve conduction velocities	Johnson et al., 1983
	5 ppm (15.6 mg/m³)	Polyneuritis	Vasilescu, 1972
	180-210 mg/m³ in 1951; lower levels later; average exposure=22 years	Electromyographic evidence of irreversible peripheral neuropathy	Corsi et al., 1983
	144-321 ppm (0.45-1.0 mg/ℓ) for ≥5 years	Polyneuritis in 88/100; tremors in 16/100; vertigo in 18/100; psychosis in 5/100; myopathy in 15/100; 43 cases of encephalopathy (autopsies on three cases revealed vascular original)	Vigliani, 1954
Cardiovascular	6 ppm (18.7 mg/m³) for 5 and 9 months	Increased systolic blood pressure at 5 months; decreasing pressure at 9 months	Kramarenko et al., 1971
	10-11 ppm (30-35 mg/m³) for ≥5 years	No effects on blood pressure or blood lipid profiles	Franco et al., 1982
	17.4 ppm	Increased blood pressure	Sakurai and Seki, 1977
	10-19 ppm (30-60 mg/m³) for ≥5 years at the start of a 15-year prospective study	Increased mortality from cardiovascular disease; risk declined to control levels upon reduction of exposure to levels <10 ppm	Nurminen and Hernberg, 1985
	19 or 39 ppm (59 or 122 mg/m³)	Changes in EKG indicative of coronary artery disease; dose-related trend toward hypertension	Cirla et al., 1978
	29 ppm (90 mg/m³) for ≥5 years	Increased mortality from coronary heart disease; increased incidence of angina	Hernberg et al., 1970; Tolonen et al., 1975
	32 ppm (100 mg/m³)	Increased cholesterol triglycerides and low-density lipoproteins in plasma	Vanhoorne, 1981
	64-161 ppm (199-503 mg/m³) up to 10 years	Vascular damage to the eye	Maugeri et al., 1966

TABLE 5-3 (cont.)

General Type of Effect	Exposure	Response	Reference
Gastrointestinal	144-321 ppm (0.45-1.0 mg/ℓ) for ≥5 years	Gastrointestinal disturbances in 28/100	Vigliani, 1954
Immunologic	3 ppm (9.3 mg/m³)	Decreased immunoreactivity	Kashin, 1965
Metabolic	20-30 ppm for >10 years	Reduced glucose tolerance	Kujalova et al., 1979

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TABLE 5-4

Summary of Subchronic Toxicity from Inhalation Exposure to Laboratory Animals

General Type of Effect	Species/Strain	Exposure	Response	Reference
Neurologic (CNS)	rat/NR	750 ppm "intermittently for 2-3 months"	Changes indicative of primary axon degeneration (multiple fusiform thickenings of central and peripheral axons)	Haltia and Linnoila, 1978a,b
	rat/Wistar	700 ppm, 6 hours/day, 5 days/week for 24 weeks	No effect on EEG	Formanek et al., 1976
	rat/Sprague-Dawley	700 ppm, 5 hours/day, 5 days/week for 12 weeks	Marked decrease in Na/K ATPase activity in brain synaptosomes	Maroni et al., 1981
	rat/Wistar	480 ppm (1.5 mg/ℓ), 5 hours/day, 6 days/week) for 1-15 months	Degeneration of myelinated fibers in spinal cord	Szendzikowski et al., 1973a
	rat/NR	5-1000 ppm up to 3 months	Review of literature; alteration of conditioned behavior	Wood, 1981
	cat/NR	2560-3210 ppm (8-10 mg/ℓ), 0.5-3 hours/day for a total of 19-74 hours over 24-92 days	Neurocellular changes in the brain ranging from chromatolysis to severe degeneration; lesions in cerebellar nuclei; capillary proliferation; hypertrophied blood vessels with swollen endothelial cells	Ferraro et al., 1941
	rabbit/NR	750 ppm "intermittently for 2-3 months"	Changes indicative of primary axon degeneration (multiple fusiform thickenings of central and peripheral axons)	Haltia and Linnoila, 1978a,b
	rabbit/NR	3 ppm (10 mg/m³) for 12 months	Increased brain acetylcholinesterase	Kulinskaya, 1967
	dog/NR	400 ppm, 8 hours/day, 5 days/week 10-15 weeks	Histologically identified lesions in the brain; ataxia; rigidity and tremors; alteration of selected reflexes	Lewey et al., 1941
	monkey/rhesus	16 ppm (50 mg/m³), 6 hours/day for 12-21 months	Degenerative changes in the cerebellum, brain stem, midbrain; bilaterally symmetrical, necrosis of the globus pallidus and zona reticulata of the substantia nigra	Richter, 1945
Neurologic (PNS)	rat/Sprague-Dawley	700 ppm, 5 hours/day, 5 days/week for 12 weeks	Decreased nerve conduction velocity after 3 weeks exposure; pathologic changes (giant axon formation) first observed in 10th week of exposure; nerve fiber degeneration with myelin sheath lesions 3 weeks after end of exposure. Recovery (regeneration of fibers) completed within 8-18 weeks after end of exposure	Colombi et al., 1981
	rat/NR	750 ppm "intermittently for 2-3 months"	Changes indicative of primary axonal degeneration (central and peripheral axons; multiple large fusiform thickenings)	Haltia and Linnoila, 1978a,b
	rat/Sprague-Dawley	750 ppm, 6 hours/day, 5 days/week for 4 months	Weakness in posterior extremities; ultrastructural changes (degeneration) in axon terminals of myoneuronal junctions	Juntunen et al., 1977

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TABLE 5-4 (cont.)

General Type of Effect	Species/Strain	Exposure	Response	Reference
Neurologic (PNS)	rat/Sprague-Dawley	750 ppm, 6 hours/day, 5 days/week for 5 weeks to 5 months	Weakness in posterior extremities; ultrastructural degenerative changes in nerves; appearance of nonspecific cholinesterase in intramuscular nerve tracts in rats with polyneuropathy	Juntunen et al., 1974
	rat/NR	192 ppm (0.6 mg/ℓ), 384 ppm (1.2 mg/ℓ), 768 ppm (2.4 mg/ℓ) or 1153 ppm (3.6 mg/ℓ), 6 hours/day, 5 days/week for 3 and 6 months	Electromyographic evidence of neuropathy at concentrations ≥384 ppm	Lukas, 1979
	rat/NR	768 ppm (2.4 mg/ℓ) or 1152 ppm (3.6 mg/ℓ), 6 hours/day, 5 days/week for 3-6 months	Electromyographic evidence of reduced conduction; elevated levels of copper in affected nerves	Lukas et al., 1980
	rat/Sprague-Dawley	700 ppm, 5 hours/day, 5 days/week for 12 weeks	Axonal swelling; increased number of neurofilaments; disappearance of neurotubules with no changes in myelin sheath	Maroni et al., 1981
	rat/Sprague-Dawley	750 ppm, 6 hours/day for 2-22 weeks; recovery for 11 weeks after exposure	Measurement of MCV in sciatic nerve 11 weeks after exposure revealed slower conduction velocity; weakness in hindlimbs	Seppalainen and Linnoila, 1976
	rat/Wistar	480 ppm (1.5 mg/ℓ) 5 hours/day for 1-14 months (intermittent sacrifices)	Swelling, spiralling and disruption of axis of long myelinated fibers of peripheral nerves; distended mitochondria; cytoplasmic vacuoles; accumulation of neurofilaments	Szendzikowski et al., 1974
	rat/NR	480 ppm (1.5 mg/ℓ) for 1-12 months	Primary axonal lesions; spinal cord damage (nerve fibers) and then changes in nerves of leg	Szendzikowski et al., 1973b
	rat/Wistar	480 ppm (1.5 mg/ℓ), 5 hours/day, 6 days/week for 1-15 months (sacrifices at monthly intervals)	Degeneration of myelinated fibers in spinal cord and peripheral nerves; paraplegia or hindlimb paralysis and muscular wasting after longer periods of exposure	Szendzikowski et al., 1973a
	rat/Wistar	288 ppm (0.9 mg/ℓ) or 512 ppm (1.6 mg/ℓ), 5 hours/day, 6 days/week for 1.5, 3, 6, 9 or 12 months	Decreased conduction velocity in sciatic and tibial nerves proportional to concentration and duration of exposure; changes were only partially reversible after exposure to 0.9 mg/ℓ for ≥6 months or to 1.6 mg/ℓ for ≥3 months	Knobloch et al., 1979
	rat/Wistar	768 ppm (2.4 mg/ℓ), 6 hours/day, 5 days/week for 6 months	Neuropathy: "formation of giant axonal swellings with concomitant degeneration of nerve fibers"; swelling of terminals from accumulation of "tubulovesicular profiles of neurofilaments"	Jirmanova and Lukas, 1984
	rabbit/NR	750 ppm intermittently for 2-3 months	Changes indicative of primary axonal degeneration (central and peripheral axons; multiple large fusiform thickenings)	Haltia and Linnoila, 1978a,b

TABLE 5-4 (cont.)

General Type of Effect	Species/Strain	Exposure	Response	Reference
Neurologic (PNS)	rabbit/NR	750 ppm, 6 hours/day, 5 days/ week for 10 weeks	Measurement of MCV of sciatic nerve 14 weeks after exposure revealed slower conduction velocity	Linnoila et al., 1974; Seppalainen and Linnoila, 1975
Cardiovascular	rat/NR	435 ppm (1.36 mg/ℓ), 4 days/ week for 12 and 26 weeks	None; endpoints included examination of glucose-6-phosphatase, alkaline phosphatase, ATPase, cholinesterase, and 5-bromoindoxylesterase activities of the arterial wall	Glinska and Korus, 1971
	rat/NR	384 ppm (1.2 mg/m³) for 4 months	Thickening of right side of the heart and aorta; increase in hexuronic acid and hexosamines in aortic wall; decrease in hydroxyproline in aortic wall	Grodetskaya et al., 1979
	rat/Wistar	256-320 ppm (0.8-1 mg/ℓ) for 4, 10, 13 months	Increased free and esterified cholesterol in aorta and skeletal muscle	Laurman and Wronsky-Nofer, 1977
	rat/Wistar	0.32, 3.2, 32 ppm (1, 10, 100 mg/m³) for "long-term"	"Cardiovascular changes" only at 32 ppm (100 mg/m³)	Saltanov et al., 1977
	rat/NR	176 ppm (0.55 mg/ℓ) for 8 months	Increases in cholesterol synthesis (liver) and serum lipid content; changes blocked by nicotinic acid administration (40 mg/kg/day for 8 months during carbon disulfide administration)	Wronska-Nofer, 1972
	rat/Wistar	313 ppm (0.96 mg/ℓ), 2.5 hours/ day, 6 days/week for 8 months or 5 hours/day, 3 days/week for 8 months	Increased cholesterol synthesis (liver); increased serum cholesterol, phospholipids and triglycerides	Wronska-Nofer and Knoblock, 1972
	rat/Wistar	320 ppm (1 mg/ℓ), 5 hours/day, 6 days/week for 6-15 months (rats were maintained on an atherogenic diet; 2% cholesterol, 0.5% cholic acid with and without thiouracil)	Increased serum cholesterol (thiouracil supplemented diet) with lipid infiltration of coronary arteries, endocardium and aorta	Wronska-Nofer et al., 1980
	rabbit/NR	141, 256 ppm (0.44, 0.8 mg/ℓ) for 3-6 months	0.44 mg/ℓ: increased phospholipid content of serum; aorta, cardiac muscle. 0.8 mg/ℓ: decreased serum phosphorus	Wesolowska, 1979
Liver	rat/Wistar	426 ppm (1.33 mg/ℓ), 5 hours/day, 4 days/week for 12 weeks; 5 hours/day, 4 days/week for 26 weeks; 10 hours/day, 4 days/week for 10 weeks	No effects on liver function; elevated levels of isozymes of lactate dehydrogenase and malate dehydrogenase in the serum; increased α-1 globulin; decreased α-2M and α-2H globulin; no changes in other liver enzymes	Gregorczyk et al., 1975
	rabbit/NR	200 ppm, 3 hours/day for 6 months	Vacuolation in cytoplasm of hepatocytes	Cuccurullo et al., 1978

TABLE 5-4 (cont.)

General Type of Effect	Species/Strain	Exposure	Response	Reference
Renal	rabbit/NR	250 ppm, 6 hours/day, 5 days/week for 16 weeks, then 500 ppm, 6 hours/day, 5 days/week, for 5 weeks, then 750 ppm, 6 hours/day, 5 days/week for 17 weeks (TWA=507 ppm)	Chronic interstitial nephritis	Cohen et al., 1959
	rabbit/NR	200 ppm, 3 hours/day for 6 months	Interstitial nephritis; tubular nephrosis; glomerulopathy	Cuccurullo et al., 1978
	rat/NR	640 ppm (2 mg/ℓ), 44 hours/week for up to 1 year	Necropsy at death revealed thickened glomerular basement membranes with hyalinosis, fatty degeneration and calcification; Bowman's capsule lined by cuboidal epithelium	Isler, 1957
	rat/NR	0.42, 3.33 ppm (1.3, 10.4 mg/m³), 4 hours/day for 6 months	Decreased urinary output; increased protein content	Salnikova and Chirkova, 1974
Renal	rat/Wistar	313 ppm (0.96 mg/ℓ), 2.5 hours/day, 6 days/week for 8 months or 5 hours/day, 3 days/week for 8 months	Increased urinary excretion of N-methylnicotinamide	Wronsky-Nofer and Knoblock, 1972
Hematologic	rat/Wistar	160 ppm (0.5 mg/ℓ), 5 hours/day, 6 days/week for 5 months	Increased RBC count; increased reticulocyte count	Kiczak et al., 1972
	rat/Wistar	160 ppm (0.5 mg/ℓ), 5 hours/day, for 5 months	Decreased fibrinolytic activity; increased soluble fibrin monomer complexes in blood	Wojewski et al., 1972
	rabbit/NR	300 ppm, 30 minutes/day for 4 months	Increased number of reticulocytes and toxic granules; reversible after termination of exposure	Wakatsuki, 1959
Gastrointestinal	rat/NR	3.2, 16.0, 32.0, 64 ppm (10, 50, 100, 200 mg/m³), 4 hours/day for 6 months	Inhibition of intestinal enzymes; disrupted glucose absorption	Murashko and Tantsyura, 1977

NR = Not reported; NOS = not otherwise stated

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velocities) of irreversible carbon disulfide-induced peripheral neuropathy (Seppalainen et al., 1972; Seppalainen and Tolonen, 1974; Vasilescu, 1972; Corsi et al., 1983; Johnson et al., 1983; Hirata et al., 1984). Johnson et al. (1983) and Hirata et al. (1984) reported that these effects occurred in men exposed to low levels of carbon disulfide (1.0-7.6 and <2 ppm, respectively).

Animals exposed repeatedly to carbon disulfide were reported to have behavioral changes (Wood, 1981), histological evidence of degenerative changes in the brain, spinal cord and peripheral nervous system (Haltia and Linnoila, 1978a,b; Szendzikowski et al., 1973a,b, 1974; Ferraro et al., 1941; Juntunen et al., 1974, 1977; Maroni et al., 1981; Lewey et al., 1941; Colombi et al., 1981; Richter, 1945; Jirmanova and Lukas, 1984), weakness, ataxia and hindlimb paralysis (Juntunen et al., 1974, 1977; Seppalainen and Linnoila, 1976; Lewey et al., 1941; Szendzikowski et al., 1973a), decreased Na/K ATPase activity in brain synaptosomes (Maroni et al., 1981), reductions in nerve conduction velocity (Lukas, 1979; Lukas et al., 1980; Seppalainen and Linnoila, 1975, 1976; Colombi et al., 1981; Knobloch et al., 1979; Linnoila et al., 1974), increased brain acetylcholinesterase activity (Kulinskaya, 1967) and the appearance of nonspecific cholinesterases in intramuscular nerve tracts (Juntunen et al., 1974).

Neurologic alterations associated with low levels of exposure including the following: brain acetylcholinesterase activity increase in rabbits (number not reported) exposed to 3 ppm for 12 months (Kulinskaya, 1967); degenerative changes in the brains of rhesus monkeys (n=4) exposed to 16 ppm, 6 hours/day for 12-21 months (Richter, 1945); and a nerve conduction velocity decrease in the sciatic and tibial nerves of Wistar rats (n=143 total) exposed to 288 ppm, 5 hours/day, 6 days/week for up to 12 months

(Knobloch et al., 1979). At 480 ppm, degenerative changes occurred in central and peripheral nerves of Wistar rats (n=80) exposed 5 hours/day, 6 days/week for up to 15 months (Szendzikowski et al., 1973a,b, 1974). In spite of histopathological alteration, reduced conduction velocities, behavioral changes and altered enzyme activities at markedly lower concentrations, Formanek et al. (1976) reported no changes in the EEG of rats exposed to 700 ppm, 6 hours/day, 5 days/week for 24 weeks.

Humans appear to be more sensitive than laboratory animals to the neurological effects of carbon disulfide. A "no-effect" level for neurological effects was not determined in any human or animal studies mentioned. In humans, occupational exposure to 1 ppm was associated with reduced nerve conduction velocity (Johnson et al., 1983) and exposure to 5 ppm was associated with polyneuritis (Vasilescu, 1972). On the basis of re-examination of subjects with neuropathy 4 years after the initial examination, Corsi et al. (1983) concluded that these neurological effects are irreversible. However, more detailed analysis of kinetics may be needed to better characterize the process of disposition/elimination of CS_2, which may help elucidate the mechanism of CS_2 neurotoxicity.

5.5.2.2. **CARDIOVASCULAR EFFECTS** -- Occupational exposure to carbon disulfide has been associated with an increased risk of mortality from coronary heart disease. NIOSH (1978) states that epidemiology studies of the viscose rayon industry "have confirmed a 2.5- to 5-fold increase in risk of death from coronary heart disease as compared with the experience of unexposed workers." Key studies in this area have been conducted by Tiller et al. (1968), Hernberg et al. (1970, 1973, 1976), Nurminen (1976), Tolonen et al. (1975, 1979) and Nurminen and Hernberg (1985). Nurminen and Hernberg (1985) conducted a 15-year prospective follow-up study of 343 male workers

employed for ≥5 years at a viscose rayon plant; a cohort of 343 male paper mill workers was chosen as a control. Cohorts were matched with respect to age, district of birth, type of job, smoking habits, level of fitness and use of medicines. For the first 7 years of the study, rayon workers were exposed to ~60 mg carbon disulfide/m³ (19.3 ppm), but exposure levels during the last 8 years of the study were reduced to ≤30 mg/m³ (≤10 ppm) because of increased concern about the toxicity of carbon disulfide. During the years when exposure was >30 mg/m³, risk of mortality from cardiovascular diseases was increased significantly (p=0.05) over controls (relative death rate = 3.2 for exposed, 1.0 for controls). As exposure levels declined to <30 mg/m³, risk declined to control levels (relative death rate = 1.0). Nurminen and Hernberg (1985) cautioned against defining 30 mg/m³ (10 ppm) as the threshold for carbon disulfide-induced cardiovascular effects since at mid-study, individuals at greater risk (hypertensive, overweight, history of cardiovascular disease) were removed to jobs where they were no longer exposed to carbon disulfide.

Occupational exposure to carbon disulfide at levels ≥6 ppm has also been associated with hypertension (Lieben et al., 1974; Sakurai and Seki, 1977; Cirla et al., 1978; Kramarenko et al., 1971), angina (Hernberg et al., 1970; Tolonen et al., 1975) and altered blood lipid profiles (Vanhoorne, 1981). Franco et al. (1982), however, found that occupational exposure at 30-35 mg/m³ for >5 years appeared to have no effect on blood pressure or blood lipid profiles in a group of 70 male viscose plant workers. In addition, Vigliani (1954) observed an encephalopathy that was vascular in origin in three men who died after occupational exposure. Maugeri et al. (1966) also reported vascular damage to the eye.

Potential cardiovascular effects (primarily changes in blood lipid profiles and cholesterol biosynthesis) were also reported in rats and rabbits exposed by inhalation to carbon disulfide (see Table 5-3); levels of exposure in these studies (32-384 ppm) were higher than levels associated with more definite evidence of cardiovascular effects in humans (10-161 ppm).

5.5.2.3. OPHTHALMOLOGICAL EFFECTS -- A majority of occupational exposure studies indicate that exposure to carbon disulfide may cause occular damage, but the exact nature of the damage is widely disputed. Sugimoto et al. (1976a,b, 1978), Goto et al. (1971, 1972), Goto and Hotta (1967) and Hotta et al. (1972) reported an association between carbon disulfide exposure and retinopathy while other investigators (Raitta and Tolonen, 1975; Raitta et al., 1974; Tolonen et al., 1977; Sugimoto et al., 1977) failed to find such an association. Raitta and Tolonen (1975), Raitta et al. (1974) and Tolonen et al. (1977) reported delayed peripapillary filling of the choroid and increased rigidity of the ocular vascular beds in workers exposed to carbon disulfide; other investigators (De Laey et al., 1980; De Laey, 1978; Evans et al., 1973) claim that these anomalies are seen in 50% of the normal population and therefore have little clinical significance with respect to carbon disulfide toxicity. De Laey et al. (1980) reported that clinically significant ocular changes in carbon disulfide-exposed individuals include abnormal electro-oculograms, sub- or supranormal electroretinograms and anomalies of the fundus (pigment alterations of the posterior pole; vascular abnormalities). Gilioli et al. (1978) reported optic disc "subatrophy" and vascular changes in the eyes of workers exposed to carbon disulfide (up to 80 ppm). Maugeri et al. (1966) reported vascular damage to the eye (indicated by altered ocular blood and humoral pressures) in workers exposed to 64-161 ppm for up to 10 years.

5.5.2.4. **HEPATIC EFFECTS** -- Reports of effects on the liver have been confined to laboratory animals. Cuccurullo et al. (1978) reported vacuolization in the cytoplasm of hepatocytes in rabbits exposed to 200 ppm carbon disulfide, 3 hours/day for 6 months. Gregorczyk et al. (1975) reported increases in α-1-globulin, plasma isozymes of lactate and malate dehydrogenase, and decreases in α-2M and α-2H globulin in rats exposed to 426 ppm carbon disulfide, 4-10 hours/day for up to 12 weeks. There were no changes in liver function test results or in other hepatic enzymes.

5.5.2.5. **RENAL EFFECTS** -- Rabbits exposed to $\geq$200 ppm carbon disulfide, 3-6 hours/day for up to 9.5 months developed interstitial nephritis, tubular nephrosis and glomerulopathy (Cohen et al., 1959; Cuccurullo et al., 1978). Glomerular changes were also identified in rats exposed to 640 ppm carbon disulfide, 44 hours/week for up to 1 year (Isler, 1957). Salnikova and Chirkova (1974) observed an increased protein content in urine accompanied by a decrease in urinary output in rats exposed to 0.42 or 3.33 ppm, 4 hours/day for 6 months. Without additional information, it is difficult to assess the adversity of this effect. Wronska-Nofer and Knobloch (1972) reported an increase in urinary excretion of N-methylnicotinamide.

5.5.2.6. **HEMATOLOGIC EFFECTS** -- Rats exposed to 160 ppm carbon disulfide, 5 hours/day, 6 days/week for 5 months or 5 hours/day for 5 months had increased RBC and reticulocyte counts and decreased fibrinolytic activity (Kiczak et al., 1972; Wojewski et al., 1972). Rabbits exposed to 300 ppm carbon disulfide, 30 minutes/day for 4 months had a reversible increase in numbers of reticulocytes and toxic granules (Wakatsuki, 1959).

5.5.2.7. **GASTROINTESTINAL EFFECTS** -- Gastrointestinal disturbances were reported in 28/100 viscose rayon workers exposed to average concentrations of 144-321 ppm carbon disulfide for $\geq$5 years (Vigliani, 1954). An

inhibition of intestinal enzymes and a disruption in glucose absorption was observed in rats exposed to 3.2-64 ppm, 4 hours/day for 6 months (Murashko and Tantsyura, 1977).

5.5.2.8. OTHER EFFECTS -- Kashin (1965) reported decreased immunoreactivity in 33.2% of 391 workers exposed to 10-16 ppm, in 25.5% of 239 workers exposed to 3 ppm carbon disulfide and in 11.5% of controls (number not reported) (U.S. EPA, 1983). Workers exposed to 10-16 ppm lost significantly more days of work (illness-related) than did controls. Individuals exposed to 3 ppm lost a greater number of illness-related workdays than did controls, but the difference was not statistically significant.

Kujalova et al. (1979) reported reduced glucose tolerance, relative to controls, in workers exposed to 20-30 ppm carbon disulfide for >10 years.

5.6. OTHER RELEVANT INFORMATION

Oral LD_{50} values for carbon disulfide are listed in Table 5-5.

5.7. SUMMARY

Animal bioassays designed to test the carcinogenicity of carbon disulfide could not be located in the available literature as cited in the Appendix. An occupational exposure study on mixed-solvent exposure (Checkoway et al., 1984; Wilcosky et al., 1984) reported an association between carbon disulfide exposure and leukemia; however, Wilcosky et al. (1984) suggested that the association may be a statistical artifact of the large number of variables examined. In another study, Nurminen and Hernberg (1984) reported that there was no association between exposure to carbon disulfide and the development of any type of cancer. Mutagenicity studies of carbon disulfide have been largely negative (Hedenstedt et al., 1979; Donner et al., 1981; NTP, 1985; Belilles et al., 1980).

TABLE 5-5

Acute Oral Toxicity of Carbon Disulfide*

Species	LD_{50} (mg/kg)
Rat	3188
Mouse	2780
Rabbit	2550
Guinea pig	2125

*Source: NIOSH, 1985

Oral teratology studies conducted in CD rats and New Zealand White rabbits (Jones-Price et al., 1984a,b) are difficult to evaluate due to maternal toxicity; however, the observation of abnormal terata (rats; 100, 200, 400 mg/kg on days 6-15 gestation) and a significant increase in the number of resorptions/litter at a level where no maternal toxicity was observed (rabbits; 25 mg/kg/day on days 6-19 gestation) suggest that carbon disulfide affects the developing fetus. Furthermore, a 3-generation inhalation teratology study using albino rats demonstrated that terata (club foot, hydrocephalus, edema, tail deformation) are observed at lower doses (0.03 or 10 mg/m^3, 8 hours/day throughout gestation) in successive generations of rats exposed to carbon disulfide (Tabacova et al., 1983).

Oral reproductive studies of carbon disulfide could not be located in the available literature as cited in the Appendix. Occupational exposure studies suggest that carbon disulfide may disturb male sexual dynamics (Cirla et al., 1978; Lancrajan et al., 1969; Lancrajan, 1972), decrease sperm count (Lancrajan et al., 1969; Lancrajan, 1972), alter the menstrual cycle and increase spontaneous abortion (Petrov, 1969; Vasileva, 1973; Cai and Bao, 1981; Bezvershenko, 1965). Inhalation studies using rats have suggested that carbon disulfide decreases ejaculated sperm count and elicits changes in male copulatory behavior (Zenick et al., 1984a,b; Tepe and Zenick, 1984). The evidence in support of carbon disulfide-induced endocrinological changes is equivocal (Lancrajan et al., 1969; Cirla et al., 1978; Maugeri et al., 1966; Wägar et al., 1983; Cirla and Graziano, 1981; Zenick et al., 1984a; Tepe and Zenick, 1984). Based on the weight of evidence presented in the studies by Tabacova et al. (1983), Lancrajan (1972) and Basileva (1973), CS_2 may pose a reproductive and developmental risk to humans at levels lower than the current threshold value (20 ppm or 62 mg/m^3). In contrast, studies by Jones-Price et al. (1984) and Belilles et

al. (1980), which used standard reproductive protocols, did not observe any teratological events in rats and rabbits exposed to dosages of CS_2 higher than Tabacova et al. (1983). Additional studies using multigeneration protocols are needed to better characterize the adverse effects of CS_2 exposure.

Only two subchronic oral studies were located in the available literature. In the first study, Wistar rats treated by gavage with 25 mg carbon disulfide/kg bw for 60 days developed normochromic or monocytic anemia, eosinopenia and reticulocytosis (Pilarska et al., 1973). In the second study, Wistar rats treated by gavage with either 0.3 mg carbon disulfide/kg bw, 2 times/week for 8 weeks or 0.6 mg carbon disulfide/kg bw for 4, 8, 12 or 20 weeks had histologically-defined damage to nerve fibers in the brain (Dietzmann and Laas, 1977). Since lower doses were not used in either study, a NOEL was not defined.

Subchronic animal inhalation studies demonstrated that carbon disulfide causes neurological effects (Haltia and Linnoila, 1978a,b; Formanek et al., 1976; Maroni et al., 1981; Szendzikowski, 1973a,b, 1974; Ferraro et al., 1941; Wood, 1981; Knobloch et al., 1979; Linnoila et al., 1974; Seppalainen and Linnoila, 1975, 1976; Jirmanova and Lukas, 1984; Juntunen et al., 1974, 1977; Lukas, 1979; Lukas et al., 1980; Kulinskaya, 1967; Lewey et al., 1941; Colombi et al., 1981; Richter, 1945); cardiovascular effects (Grodetskaya et al., 1979; Laurman and Wronska-Nofer, 1977; Saitanov et al., 1977; Wronska-Nofer, 1972; Wronska-Nofer and Knobloch, 1972; Wronska-Nofer et al., 1980; Wesolowska, 1979); hepatic effects (Gregorczyk et al., 1975; Cuccurullo et al., 1978); gastrointestinal effects (Murashko and Tantsyura, 1977); renal effects (Cohen et al., 1959; Cuccurullo et al., 1978; Isler, 1957; Salnikova and Chirkova, 1974; Wronska-Nofer and Knobloch, 1972); and hematological effects (Kiczak et al., 1972; Wojewski et al., 1972; Wakatsuki, 1959).

Occupational exposure studies and case reports suggested that carbon disulfide may cause neurological effects (Vigliani, 1954, Delpech, 1856; Viscose Rayon Survey, 1938; Peterson, 1892; Hamilton, 1915; Jump and Cruice, 1904; Francine, 1904; Hanninen, 1971; Tuttle et al., 1976; Seppalainen et al., 1972; Seppalainen and Tolonen, 1974; Vasilescu, 1972; Corsi et al., 1983; Johnson et al., 1983; Hirata et al., 1984); cardiovascular effects (Tiller et al., 1968; Hernberg et al., 1970, 1973, 1976; Nurminen, 1976; Tolonen et al., 1975; Nurminen and Hernberg, 1985; Vigliani, 1954; Lieben et al., 1974; Sakurai and Seki, 1977; Cirla et al., 1978; Kramarenko et al., 1971; Franco et al., 1982); ophthalmological effects (Sugimoto et al., 1976a,b, 1978; Goto et al., 1971, 1972; Goto and Hotta, 1967; Hotta et al., 1972; Raitta and Tolonen, 1975; Raitta et al., 1974; Tolonen et al., 1977; Sugimoto et al., 1977; De Laey et al., 1980; De Laey, 1978; Evans et al., 1973; Gilioli et al., 1978; Maugeri et al., 1966); immunological effects (Kashin, 1965); gastrointestinal effects (Vigliani, 1954); and metabolic effects (Kujahova et al., 1979).

In humans as well as in animals, neurological effects occur at the lowest levels of exposure (<2 ppm in humans). A NOEL for chronic toxicity has not been defined in either inhalation studies in animals or in occupational exposure studies.

6. AQUATIC TOXICITY

6.1. ACUTE

The available information concerning the acute toxicity of carbon disulfide to aquatic organisms is summarized in Table 6-1. Because different responses were monitored in the various studies, it is difficult to compare results and identify sensitive species. In general, the limited data indicate that carbon disulfide concentrations of 30-250 mg/ℓ are acutely toxic to fish.

Pertinent data regarding the acute toxicity of carbon disulfide to aquatic invertebrates could not be located in the available literature as cited in the Appendix.

6.2. CHRONIC

Pertinent data regarding chronic toxicity of carbon disulfide to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding the effects of carbon disulfide on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding carbon disulfide residues in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

There is very little information available concerning the toxicity of carbon disulfide to aquatic biota. The available data indicate that concentrations of 30-250 mg/ℓ are toxic to most fish species. No data concerning chronic toxicity, plant effects or residues were located in the available literature.

TABLE 6-1

Acute Toxicity of Carbon Disulfide to Fish

Species	Concentration (mg/ℓ)	Response	Reference
Perch Perca sp.	35	toxicity threshold	Meinck et al., 1956
Bleak Alburnus alburnus	35	toxicity threshold	Meinck et al., 1956
	65	96-hour LC_{50}	Bengtsson and Tarkpea, 1983
Golden orfe Leucissus idus	25, 164 95, 265 126, 290	48-hour LC_0 48-hour LC_{50} 48-hour LC_{100}	Juhnke and Luedemann, 1978
Mosquitofish Gambusia affinis	<100 135 162 180	no effect, 96 hours 48- and 96-hour LC_{50} 24-hour LC_{50} 100% mortality, 48 hours	Wallen et al., 1957
Orangespotted sunfish Lepomis humilis	100-127	lethal in 1 hour	Shelford, 1917
Rainbow trout Salmo gairdneri	5000	7-minute exposure resulted in 100% mortality within 48 hours after transfer to clean water	Ellis, 1937

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The OSHA standard for occupational exposure to carbon disulfide (8-hour TWA) is 20 ppm with an acceptable ceiling of 30 ppm (CFR, 1983). ACGIH (1985) recommends a TLV of 10 ppm. Environ, Inc. (1984) recommended an ADI of 0.2 mg/kg/day, based on a 12-month inhalation LOEL (0.9 mg/ℓ or 288 ppm) for reduced nerve conduction velocity in rats.

7.2. AQUATIC

Pertinent data regarding aquatic guidelines and standards for carbon disulfide could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Carbon disulfide has not been tested for carcinogenicity in mammals and the National Toxicology Program has not scheduled it for testing (NTP, 1985). Although both Checkoway et al. (1984) and Wilcosky et al. (1984) reported an association between occupational exposure to carbon disulfide and leukemia, the association may be a statistical artifact. Nurminen and Hernberg (1984) reported that there was no association between occupational exposure to carbon disulfide and cancer of any kind. Mutagenicity tests have yielded primarily negative results (Hedenstedt et al., 1979; Donner et al., 1981; NTP, 1985; Belilles et al., 1980).

The only two subchronic oral studies available yielded LOAELs but no NOAEL. Pilarska et al. (1973) observed anemia in Wistar rats treated by gavage with carbon disulfide at 25 mg/kg bw/day for 60 days. Dietzmann and Laas (1977) observed degenerative changes and localized histoenzymatic changes in the brains of Wistar rats treated by gavage with carbon disulfide at 0.06 mℓ, twice weekly for 8 weeks followed by 0.12 mℓ, twice weekly for 12 weeks. Twice weekly treatment resembles a repeated acute exposure protocol much more than it does a well executed subchronic study, and this study is not, therefore, recommended for use in deriving an ADI.

In an oral teratogenicity study in rats, maternal toxicity was observed at 100 mg/kg/day, the lowest level tested, and fetotoxicity, manifested as reduced fetal body weight, occurred in a dose-related fashion at 200-600 mg/kg/day (Jones-Price et al., 1984a). When exposed to carbon disulfide, rabbits appear to be more sensitive than rats to the effects of carbon disulfide. When carbon disulfide is given at 25, 75 or 150 mg/kg/day, maternal toxicity occurred at 75 mg/kg/day, but a dose-related increase in fetal resorption occurred at all dose levels (Jones-Price et al., 1984b).

An increased incidence of fetal malformation was observed in all treated groups of rabbits, but the increase became statistically significant only at 150 mg/kg/day, the highest level tested.

The inhalation toxicity of carbon disulfide has been studied more intensively than oral toxicity. Several types of biological effects, including neurological, cardiovascular, reproductive, immunological, gastrointestinal and metabolic have been noted in experimental animals and humans. Generally, humans appear to be more sensitive than animals and, in humans, the nervous system appears to be the most sensitive target, as neurologic effects have been noted at <2 ppm (6.2 mg/m³) in occupational exposure (Hirata et al., 1984).

The sensitivity of the human reproductive processes and the human fetus to occupational exposure to carbon disulfide is difficult to assess, but concentrations of 12 and 13 ppm have been associated with disruptions to female (Cai and Bao, 1981) and male (Lancrajan et al., 1969; Lancrajan, 1972) reproduction, respectively. In a 3-generation teratogenicity study using rats (Tabacova et al., 1983), a statistically increased incidence of terata was observed at 50 mg/m³ but not 10 mg/m³ in the F_1 generation, and at 0.03 mg/m³, the lowest concentration tested, in the F_2 generation. The authors speculated that prenatal exposure to carbon disulfide may have permanently altered xenobiotic metabolism resulting in more serious effects at lowered thresholds in subsequent generations.

The repeat-dosing F_0-F_2 teratology study by Tabacova et al. (1983) yielded the lowest level of exposure at which effects were seen (0.03 mg/m³). However, Tabacova et al. (1983) reported incidences of terata using the fetus as the unit; terata incidences per litter(s) were not reported. For instance, the F_2 0.03 mg/m³ exposure group had an

incidence of 14/124 (11.3%) vs. a control incidence of 0/204 ($p<0.0001$) using the Fisher Exact test. As discussed by Weil (1970), the litter may be a more appropriate unit for the measurement of teratogenic response because the use of the fetus as the unit exaggerates the significance of the test result by erroneously inflating the number of independent sampling units. Inhalation studies conducted in the United States (Choudhury and Manson, 1981; Hardin et al., 1981) at much higher levels of exposure with carbon disulfide using rats and rabbits did not show developmental defects in either species tested. Using recommended teratology testing protocols, the U.S. studies were conducted in different laboratories under adequately controlled environment. Despite apparent dose-response relationships of carbon disulfide and fetal malformations reported by Tabacova et al. (1983), the absence of teratological events in well-controlled U.S. studies suggest further testing of CS_2 by using multigeneration protocols to better characterize the adverse effects of CS_2 exposure.

Given that the quality and quantity of oral studies are extremely limited, that effects seen in the subchronic oral studies (neurological and hematological effects) were also seen in inhalation studies and that an oral multigeneration teratology study has not been conducted, the inhalation data should be considered in the derivation of an oral ADI.

The data reported in the Hardin et al. (1981) study were generated at Litton Bionetics, Maryland (under contract for NIOSH). Rats and rabbits were exposed to 20 ppm or 62.3 mg/m³ (recommended occupational exposure limit) and 40 ppm or 124.6 mg/m³ of carbon disulfide during the entire length of the pregnancy period and also 3 weeks before breeding to simulate occupational exposure. Despite levels of carbon disulfide tested at much higher levels than the Bulgarian studies (Tabacova et al., 1983), adverse

effects of carbon disulfide on maternal/fetal toxicity and fetal malformations were not observed in rats or rabbits exposed to either 20 or 40 ppm carbon disulfide. While evaluating the NIOSH-sponsored study (Hardin et al., 1981) it was discovered that there was a high incidence of mortality in rabbits exposed pregestationally and either 0-18 or 6-18 days of gestation to 20 ppm CS_2; however, the incidence in the group similarly exposed to 40 ppm was no greater than controls. Additionally, rats in this study had an outbreak of SDA virus infection during acclimatization period. Despite these incidental problems, the histopathological examinations at terminal sacrifice did not reveal an underlying disease state; deaths unrelated to CS_2 exposure. The NCTR/NTP study (Jones-Price et al., 1984a,b) observed 25 mg/kg in rabbits as an AEL (fetal resorption). Fetotoxicity and fetal malformation in this study were not observed in rats at the lowest level (100 mg/kg) of carbon disulfide exposure. Based on the methodology of U.S. EPA (1980) the observed no-effect levels in rats or rabbits following inhalation exposure to 62.3 or 124.6 mg/m³ carbon disulfide can be estimated as 5 and 10 mg/kg/day for rats and 11 and 22 mg/kg/day for rabbits [by using conversion factors: 6 hours/24 hours, 1.6 m³/day (rabbit) or 0.224 m³/day (rat) breathing rate; 1.13 kg (rabbit) or 0.35 kg (rat) bw and 0.5 absorption rate]. The highest NOEL from the Hardin et al. (1981) study, 22 mg/kg/day in the rabbit, should not be used for an ADI estimate because adverse effects were seen in rabbit fetuses following oral exposure of pregnant does to 25 mg/kg carbon disulfide. Therefore, the highest NOEL that is below an effect level is the estimated low dose of 11 mg/kg/day in rabbits. By applying an uncertainty factor of 100 (10-fold adjustments of both the expected intra- and interspecies variability to the toxicity of this compound in lieu of chemical-specific data), a provisional ADI of 0.1

mg/kg/day or 8 mg/day for a 70 kg person is recommended. Note that the usual factor of 10 S (subchronic to chronic extrapolation) is not used here since the exposure duration covered the entire critical period for the elicitation of the critical effect. Further, the ADI of 0.1 mg/kg/day has been verified by the U.S. EPA Reference Dose Work Group of the Agency-wide Risk Assessment Forum which convened on July 8, 1985 (U.S. EPA, 1986).

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Data pertaining to the teratogenicity, reproductive toxicity and chronic toxicity of carbon disulfide were discussed in Chapter 5 and summarized in Tables 5-1 to 5-4 and Table 9-1. Because of the large number of studies available, details such as sex, body weight and numbers of animals are not included in the tabular summaries. Furthermore, since the choice of study that will yield the highest CS is obviously the study with the lowest level of exposure (highest RV_d) and the most severe effect (teratogenicity, rating an RV_e of 10), transformed doses were not included in the tables.

The 3-generation inhalation teratology study by Tabacova et al. (1983) yields the lowest level of exposure at which adverse carbon disulfide-induced effects are observed. A dose-related increase in teratogenic effects (hydrocephalus, microencephaly, club-foot, tail deformation, hypognathia) was observed in F_2 progeny of F_1 rats exposed to 0, 0.03, 10, 100 or 200 mg carbon disulfide/m³ in utero and throughout gestation. The incidence of these effects was statistically significant at all levels of exposure. No evidence of maternal toxicity was observed at 0.03 mg/m³. Tabacova et al. (1983) reported incidences of terata using the fetus as the unit. As discussed by Weil (1970), the litter may be a more appropriate unit for the measurement of teratogenic response because the use of the fetus as the unit exaggerates the significance of the test result by erroneously inflating the number of independent sampling units.

The NCTR/NTP study (Jones-Price et al., 1984a,b) employed different oral doses of carbon disulfide in both rats and rabbits during their respective organogenesis periods. The carbon disulfide doses used in this study were considerably higher than the LOAEL (estimated as 0.01 mg/kg/day) of the

TABLE 9-1

Summary of Subchronic Toxicity to Wistar Rats from Oral Exposure

General Type of Effect	Exposure	Response	Reference
Neurologic	0.06 mℓ/rat (0.3 mg/kg bw), 2 times/week for 8 weeks, then 0.12 mℓ/rat (0.6 mg/kg bw), 2 times/week for 12 weeks	Histologically identified damage to nerve fibers in the brain and spinal cord; reductions in activities of glutamate dehydrogenase and arylsulfatase (entire brain), and of succinic dehydrogenase and acetylcholinesterase (only in areas of elective parenchyma necrosis)	Dietzmann and Laas, 1977
Hematologic	25 mg/kg/day for 60 days	Normochromic and normocytic anemia; eosinopenia; reticulocytosis	Pilarska et al., 1973
Teratogenic effect	25 mg/kg/day for 6-19 days (rabbit)	Incidence of fetal malformations	Jones-Price et al., 1984a

Bulgarian study. Maternal toxicity was observed at 75 or 100 mg/kg/day in rabbits or rats, respectively, whereas a dose-related incidence of fetal malformation was observed in all treated groups of rabbits; this incident became statistically significant only at 150 mg/kg/day, the highest level tested. A subchronic oral toxicity study in rats (Pilarska et al., 1973) provided supportive evidence; carbon disulfide at 25 mg/kg/day produced reversible anemia in Wistar rats. Therefore, the lowest dose of carbon disulfide (25 mg/kg/day) that produced fetal malformations in rabbits (Jones-Price et al., 1984b) can be used to calculate a CS (Table 9-2). The most severe effect, teratogenicity without maternal toxicity, resulted in an RV_e of 10. The animal dose of 25 mg/kg can be converted to the chronic human MED of 442.9 mg/day [25 mg/kg x $(1.13/70)^{1/3}$ x 70 kg], which resulted in an RV_d of 1.5 and a CS of 15 (RV_e 10 x RV_d 1.5) (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Carbon disulfide has not been tested for carcinogenicity in mammalian systems and the National Toxicology Program has not scheduled it for testing (NTP, 1985). In a study of multisolvent exposure, Checkoway et al. (1984) and Wilcosky et al. (1984) reported an association between occupational exposure to carbon disulfide and leukemia. Wilcosky et al. (1984) recognized that the presumed class of causative agents, solvents is a "mixed group of compounds," of which benzene is generally a minor quantitative compound. The usage of solvents has varied qualitatively and quantitatively over time with considerable temporal overlap of exposures. Consequently, Checkoway et al. (1984) commented that the identification of the specific agent(s) responsible for leukemia excesses is likely to be a complicated process requiring investigator(s) judgment as to which solvents are likely to be leukemogenic based on previous experimental and human observational

TABLE 9-2

Oral Composite Score for Carbon Disulfide in New Zealand Rabbits*

Animal Dose	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
25 mg/kg/day	442.9	1.5	teratogenic effects; no maternal toxicity	10	15	1000

*Source: Jones-Price et al., 1984b

TABLE 9-3

Carbon Disulfide

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	442.9 mg/day
Effect:	teratogenic effects; no maternal toxicity in rabbits
Reference:	Jones-Price et al., 1984b
RV_d:	1.5
RV_e:	10
Composite Score:	15
RQ:	1000

*Equivalent human dose

data. In a 15-year prospective follow-up study, Nurminen and Hernberg (1984) failed to determine a relationship between exposure to carbon disulfide and any type of cancer. Based on the lack of positive evidence of carcinogenicity, carbon disulfide is best classified as an IARC Group 3 compound. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment and unavailability of human data and inadequate animal data, the overall weight of evidence classification is Group D, meaning carbon disulfide cannot be classified as a human carcinogen. According to the hazard ranking classification, the Group D classification with an RQ of 1000 cannot be assigned to a hazard ranking scheme.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

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